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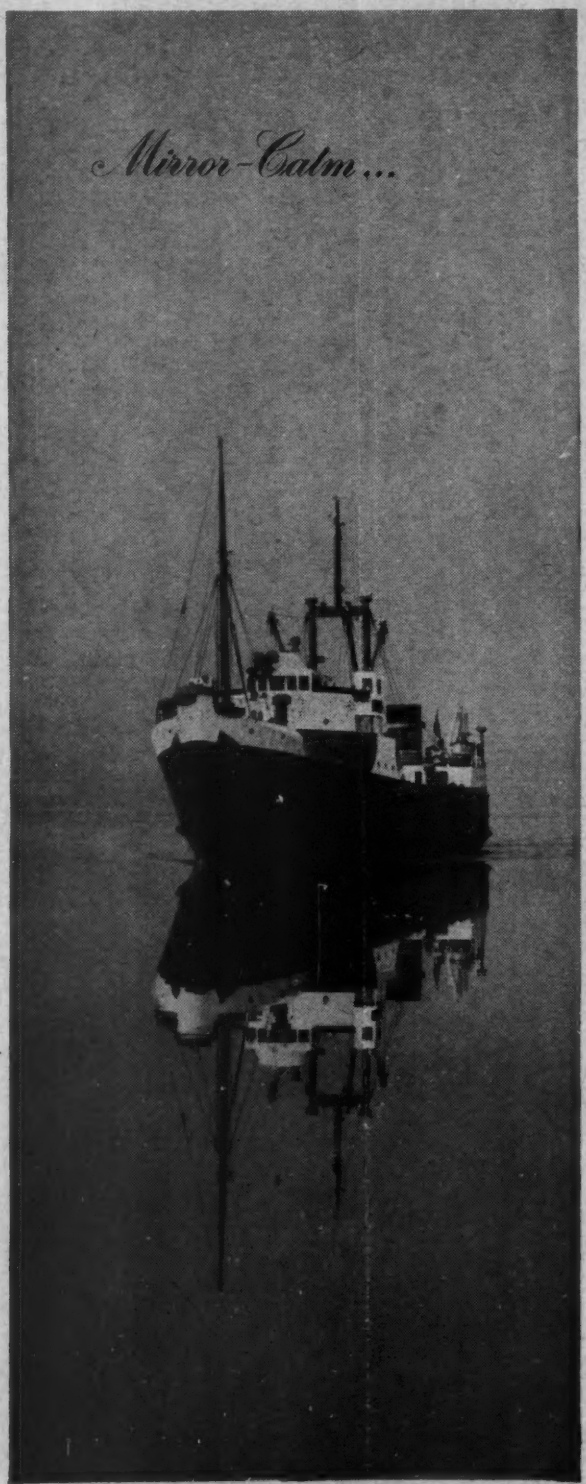

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LONDON SATURDAY OCTOBER 7 1961

SEROLOGICAL OVERLAP BETWEEN LUPUS ERYTHEMATOSUS, RHEUMATOID ARTHRITIS, AND THYROID AUTO-IMMUNE DISEASE

BY

W. HIJMANS, M.D.
Department of Rheumatology, the University Hospital, Leyden

D. DONIACH, M.D.
Institute of Clinical Research, the Middlesex Hospital Medical School, London

I. M. ROITT, D.Phil.
Courtauld Institute of Biochemistry, the Middlesex Hospital Medical School, London

AND

E. J. HOLBOROW, M.D.
Medical Research Council Rheumatism Research Unit, Canadian Red Cross Memorial Hospital, Taplow, Maidenhead

Circulating auto-antibodies are being reported in an increasing number of diseases, but their role in the pathogenesis of these disorders is far from clear. The clinical interrelationships and the serological overlap between the "auto-immune" diseases is of particular relevance to the understanding of the fundamental disturbances underlying these phenomena. The occasional finding of L.E. cells in patients with thyroid disorders (Wilkinson and Sacker, 1957; Hijmans *et al.*, 1958; Thomas, 1959; White, 1959) and the clinical association of connective-tissue diseases with Hashimoto's thyroiditis (Short *et al.*, 1957; Luxton, 1956; Beare, 1958; Doniach and Roitt, 1959; Heaton, 1959) prompted us to undertake an investigation into the incidence of thyroid antibodies in systemic lupus erythematosus, rheumatoid arthritis, and allied conditions on the one hand, and on the other hand to determine the frequency with which antinuclear factors, as shown by the presence of L.E. cells, fluorescent nuclear staining (A.N.F. test), and nuclear complement fixation occur in patients with diffuse auto-immune thyroiditis.

Since the initiation of this study other authors have reported on the association of Hashimoto's disease with systemic lupus (White *et al.*, 1961), lupoid hepatitis (Mackay and Perry, 1960), Sjögrens's syndrome (Bloch *et al.*, 1960; Bunim, 1961), and rheumatoid arthritis (Buchanan *et al.*, 1961). These recent papers also deal with the presence of circulating thyroid antibodies in patients with connective-tissue diseases (see also Goodman *et al.*, 1960; Jansz, 1960).

Materials and Methods

Clinical Material

The patients were drawn mainly from the three hospitals taking part in this study, but in addition sera were received for antibody tests from many other centres. Three main disease groups were studied, in addition to control groups.

1. *Systemic Lupus Erythematosus* (*S.L.E.*) (65 cases).—The patients all had systemic manifestations, and we excluded from this group cases of clinical rheumatoid arthritis in which L.E. cell tests were positive. The group consisted of 59 females aged 14–76, with a mean age of 45 years, and 6 males aged 34–76, with a mean age of 55 years. In five of the female patients there was an associated thyroiditis which was clinically overt in three cases, and in the other two was diagnosed only after examination of the thyroid with special function tests. These five cases of combined disease were treated as a subgroup to avoid selection bias.

2. *Rheumatoid Arthritis* (*R.A.*) (86 cases).—These were all "definite" or "classical" cases as defined by the American Rheumatism Association (Ropes *et al.*, 1959). They included cases with negative latex or sheep-cell agglutination tests, and also cases with positive L.E. cell tests. There were 75 females and 11 males, ranging in age from 24–73, with a mean age of 52 years. Six of the patients had colloid goitre, one was thyrotoxic, and seven cases had primary myxoedema or Hashimoto's disease. The seven cases of combined rheumatoid arthritis and thyroiditis were considered as a subgroup, since they were probably selected from a large rheumatoid arthritis population.

3. *Hashimoto's Disease and Primary Myxoedema* (182 cases).—These were selected for their high antibody levels, but had no overt connective-tissue disease. A few of the patients had thyrotoxicosis with a well-marked superimposed thyroiditis. The female-to-male ratio was 12:1 and the mean age was 51 years.

4. *Controls.*—The incidence of positive reactions for each of the antibody tests employed was previously established in healthy and diseased controls at each of the laboratories, so that different individuals make up the control group for each method.

In addition to these main groups we collected seven cases of combined liver disease and lymphadenoid goitre or myxoedema. These cases were included in the present study in view of the relation of certain cases of hepatitis with lupus erythematosus and the known histological association of thyroiditis with cirrhosis in post-mortem studies (Bastenie, 1937; McConkey and Callaghan, 1960). We also examined 83 cases of Sjögren's syndrome for thyroid antibodies and anti-nuclear factors (in collaboration with J. Heaton and Barrie Jones) and the detailed results of this will be published separately.

Sera.—These were stored at −20° C. for up to three years before the tests were performed. Repeated thawing and freezing of the specimens could not always be avoided.

Serological Methods

L.E. Cell Tests.—Preparations were made according to Zimmer and Hargraves (1952) except for an incubation time of 10 minutes between fragmentation of the blood clot and centrifugation. Where only serum was available the indirect test of Kievits and Schuit (1957) was used.

Nuclear Complement Fixation.—This was performed with chicken erythrocyte nuclei, and the titre was recorded as the reciprocal of the highest serum dilution giving total inhibition of haemolysis using 2 M.H.D. of complement as described previously (Hijmans and Schuit, 1959). Some of the sera were also tested with D.N.A., calf thymus nucleoprotein, and nuclear histone.

Fluorescent Test for Anti-nuclear Factors (A.N.F.).—The indirect (sandwich) technique was used as described by Weir, Holborow, and Johnson (1961). Sections of frozen, unfixed, fresh post-mortem human infant thyroid, or of thyrotoxic thyroid glands obtained at operation, were used as the nuclear substrate. The tests were done at room temperature, but positive Hashimoto and S.L.E. sera were retested at 37° C. (Couchman *et al.*, 1961).

Latex Fixation Test: for Rheumatoid Factor (R.F.).—This was done by the method of Singer and Plotz (1956), using whole serum. Some of the R.A. sera were tested by the Rose-Waaler differential sheep-cell agglutination test (D.A.T.).

Thyroid Antibody Tests.—Three organ-specific auto-antigens are so far known to be implicated in thyroiditis: thyroglobulin, CA2 (second antigen of the thyroid colloid) and the microsomal antigen of thyroid cells. Antibodies to thyroglobulin were detected by the tanned-red-cell (T.R.C.) agglutination test, using formolized sheep cells coated with thyroglobulin (Fulthorpe *et al.*, 1961), and the precipitin test in agar. CA2 antibodies fail to react in these tests and can be detected only by the Coons technique, using frozen thyroid sections fixed in methanol (Balfour *et al.*, 1961). The microsomal antibody was titrated by the complement-fixation test (C.F.T.) using crude thyrotoxic gland extracts and 2 M.H.D. of complement (Roitt and Doniach, 1958). All S.L.E. and R.A. sera reacting with crude thyroid extract were retested with microsomal preparations obtained by differential centrifugation of disrupted thyrotoxic gland homogenates. The organ specificity of the C.F.T. reactions was further checked by cytoplasmic staining of unfixed, frozen thyroid sections with the Coons fluorescent sandwich technique (Holborow *et al.*, 1959). The cytoplasmic fluorescent test is an important check for sera giving high-titre non-organ-specific complement fixation (A.I.C.F. reaction, see below), since microsomal preparations can be contaminated with soluble non-specific antigens which would react in C.F.T. However, A.I.C.F. reactors do not stain the thyroid cytoplasm. In the presence of concomitant bright nuclear fluorescence, it is difficult to judge weak cytoplasmic staining and A.N.F. positive sera should be first absorbed with nuclei, but this has not yet been done.

Auto-immune Complement Fixation Reaction (A.I.C.F.).—This non-organ-specific complement fixation reaction is obtained with human thyroid extracts as well as with human liver or kidney, and the test can be done equally well with rat organs (Gajdusek, 1958; Hackett *et al.*, 1960). All sera giving positive C.F.T. with thyroid were tested in parallel using 1/10 saline extracts of human post-mortem liver and 2 M.H.D. of complement.

Cell Fractionation Studies.—Selected S.L.E. and Hashimoto sera were further tested by C.F.T. with subcellular liver fractions obtained by differential centrifugation (Schneider and Hogeboom, 1950) to determine the heterogeneity of antigens reacting in the A.I.C.F. test.

Results

The incidence of positive serological reactions in the three main groups of patients, and the subgroups of mixed disease together with controls, are shown in Table I. Sera were recorded as having thyroid antibodies when they were positive with one or more of the tests, using specific thyroid antigens.

TABLE I

Clinical Diagnosis	No. of Patients in Series	Incidence of Positive Reactions				
		Thyroid	L.E. Cells	A.N.F.	A.I.C.F. titre ≥ 1 : 16	R.F. Latex Test
Systemic lupus erythematosus	60	15/60 (25%)	59/60 (98%)	59/60 (98%)	22/60 (37%)	20/50 (40%)
S.L.E. + Hashimoto ..	5	5/5	5/5	5/5	4/5	0/5
Rheumatoid arthritis	79	9/79 (11%)	16/79 (20%)	40/79 (50%)	7/72 (10%)	35/64 (55%)
R.A. + Hashimoto	7	7/7	0/7	3/7	1/7	5/7
Hashimoto's disease (uncomplicated)	182	182/182 (100%)	0/110	14/182 (8%)	9/182 (5%)	2/98 (2%)
Controls ..	Composite groups	10%	0%	2%	<1%	2 to 5%

Systemic Lupus

The group of 65 S.L.E. patients (including the five cases with associated thyroiditis) all had positive L.E. cell tests, and the A.N.F. reaction was positive in all but one who was tested when the disease was in remission two years after the L.E. cell test had last been found positive. Thyroid-specific antibodies of high titre were found only in the five cases with diffuse thyroiditis. Of the 60 cases without overt thyroid disorder, 12 gave T.R.C. agglutination titres varying from 1/5 to 1/2500. In all these cases the agglutination reactions could be considered specific since they were inhibited by adding human thyroglobulin to the sera, and were negative when tanned cells coated with sheep thyroglobulin were used.

CA2 antibodies were found in several of the T.R.C. and C.F.T. positive cases and also in three patients having no other thyroid antibodies. In two further patients C.F.T. was positive to a titre of 1/8 with thyroid extract and negative with liver. However, the organ specificity here is not absolutely certain, since the A.I.C.F. reaction is not always obtainable consistently with liver extracts from different individuals. In view of this doubt, these two cases have been excluded, so that definitely thyroid-specific antibodies were found in 15/60 S.L.E. patients without overt thyroiditis. Positive results were entirely confined to the female patients.

Rheumatoid factor was present in 20/55 S.L.E. cases tested, and non-organ-specific A.I.C.F. reactions were obtained in 26 of the 65 cases.

Rheumatoid Arthritis

Of the 86 rheumatoid arthritis patients, 16 had positive L.E. cell tests and A.N.F. was found in 43. Results of tests for thyroid antibodies in this group are shown in Table II. As in the former group, high titres were found only in the seven patients with associated myxoedema or Hashimoto's disease. Of the remaining

TABLE II.—*Incidence of Thyroid Antibodies in R.A. Patients With and Without Thyroid Involvement*

	Thyroid Antibodies		Totals
	+	−	
Without colloid goitre or thyrotoxicosis	6	66	72
With colloid goitre or thyrotoxicosis ..	3	4	7
,, Hashimoto's thyroiditis	7	0	7

79 cases, nine gave positive tests, all of low titre. Three of these belonged to a group of seven cases associated with colloid goitre or thyrotoxicosis. The other six were in the group of 72 rheumatoid arthritis patients without thyroid involvement. This incidence corresponds closely with that found in non-rheumatoid groups—that is, the presence of colloid goitre increases the likelihood of thyroid antibodies from the normal of about 10% in females of that age group to 30–40%. Latex sheep-cell tests were positive in 39 of 70 cases tested, and A.I.C.F. titres of 1/16 or over were obtained in 8 of 78 cases tested, one occurring in a patient with combined R.A. and Hashimoto's thyroiditis.

Hashimoto's Disease

The 182 uncomplicated Hashimoto cases had negative L.E. cell tests, mostly done by the indirect method. Nuclear complement-fixation tests were also negative in 100 cases tested. Weak antinuclear reactions were obtained by the Coons technique in 14 of 182 cases when the staining procedure was carried out at room temperature. These sera were positive in low titre, in the range 1/10 to 1/20, and when the tests were repeated at 37° C. reactions became very weak or negative. (Couchman *et al.*, 1961, have noted this effect with some A.N.F. positive sera from miscellaneous hospital cases and pregnant women.) No effect of temperature on A.N.F. positivity was found with S.L.E. or R.A. sera.

The latex test for R.A. factor was positive in two of 98 uncomplicated Hashimoto cases tested and was positive in four of the seven patients with combined R.A. and myxoedema or Hashimoto's disease. A.I.C.F. reactions against human liver were found in 7% of the 182 thyroiditis cases tested, and titres ranged from 1/4 to 1/32 except for one patient who gave partial fixation up to 1/128. When only titres of 1/16 or greater are considered, the incidence of A.I.C.F. in Hashimoto's disease is 5%, and the reaction was combined with a positive A.N.F. test in only one instance.

Control Groups

A recent hospital population study (Hill, 1961) using our T.R.C. and C.F.T. methods showed an incidence of 10% thyroglobulin antibodies in women aged between 40 and 60. Using 2 M.H.D. of complement and 1/4 dilution of serum, we have found no thyroid-specific complement-fixing antibodies in non-thyroid patients, but if the Coons technique with neat serum is employed cytoplasmic staining is found in 8% of middle-aged women. A.I.C.F. reactions were found in less than 1% of a mixed hospital population, but exact figures are difficult to give owing to variability of the antigens. The A.N.F. test gave weak positive results in 2 out of 132 normal sera and in 2 out of 65 cases of pulmonary tuberculosis tested at Taplow using infant thyroid, and in 18 out of 560 (3.2%) mixed thyroid patients excluding Hashimoto and myxoedema at the Middlesex Hospital, using fresh thyrotoxic thyroid as substrate. The latex test in our hands gives positive results in <2% of patients showing no joint disease. The L.E. cell test performed in Leyden gave negative results in over 3,000 normal subjects and mixed hospital patients.

TABLE III.—*Serological Findings in Seven Cases of Combined Liver and Thyroid Disease*

Case	Sex and Age	Diagnosis	Nuclear Antibodies		Thyroid Antibodies			A.I.C.F.	Rh Factor
			L.E. Cells	A.N.F.	T.R.C.	Pptin.	C.F. Titre with Thyroid Microsomes	C.F. Titre with Liver Microsomes	Latex
1	F 66	Cirrhosis+Hash. dis.	−	±	2,500	+	128	−	−
2	F 40	Lupoid hepatitis+myxoedema	+	±	2½ m.	+	32	−	−
3	F 43	Cirrhosis+Hash. dis.	−	−	2½ ,,	+	>512	64	−
4	F 28	Lupoid hepat.+myx.	+	−	2½ ,,	−	32	32	−
5	M 70	Prog. hepat.+Hash. dis. ..	n.d.	−	2½ ,,	+	128	64	+
6	F 43	Lupoid hepat. pulm. fibrosis, +Hash. dis.	+	−	− (CA2+)	−	128	32	−
7	F 50	Cirrhosis+Hash. dis.	n.d.	n.d.	25,000	+	−	4	n.d.

n.d.=Not done.

TABLE IV.—*Comparison of Complement Fixation Reactions with Subcellular Fractions of Human Liver and Thyrotoxic Thyroid*

Case	Clinical Diagnosis	Thyroid		Liver				Remarks
		Whole Homogenate	Micro-somes	Nuclei	Mito-chondria	Micro-somes	Super-natant	
1	S.L.E.	32	0	32	512	128	512	
2	,, ...	⩾512	512	⩾512	⩾512	⩾512	128	T.R.C. titre 2,500. Patient not avail. for clin. invest
3	,, ...	128	—	—	—	—	128	Serum anti-complementary to 1:32
4	,, ...	128	0	16	128	0	32	
5	,, ...	256	0	0	128	32	16	
6	,, ...	512	0	0	256	16	512	
7	R.A.	256	0	0	256	256	256	L.E. cells
8	Lupoid hepatitis+myxoed.	32	32	8	256	32	0	L.E. cells Thyr. pptin.
9	Cirrhosis	512	0	0	>512	>512	>512	
10	? Mild L.E.	64	0	8	>512	256	8	A.N.F.+L.E. cells. Low serum complement
11	Post-op. colloid goitre ..	>512	0	0	>512	>512	>512	A.N.F. negative. No symptoms
12	Hash. dis.	>512	32	8	32	8	>512	T.R.C. titre 25,000
13	Toxic Hash. goitre: malig. exophth.	>512	>512	0	8	8	0	Thyr. pptins.
14	Hash. dis.	128	16	64	>512	256	16	,, ,,

Liver Disease With Overt Thyroiditis

The seven patients in this group all had progressive hepatitis or cirrhosis of unknown origin with liver failure. Five also had Hashimoto goitres and two had myxoedema without thyroid enlargement. Details of serological findings are shown in Table III. Thyroid-specific antibodies were of high titre, and five out of seven cases also gave C.F.T. with human liver. Three of the cases had given occasional positive L.E. cell preparations, but were subsequently treated with cortisone, and we were not able to obtain convincing A.N.F. results on the specimens taken after prolonged treatment. A more detailed analysis of sera giving C.F. reactions with thyroid and other organ extracts is presented in Table IV. The majority of the S.L.E. sera were negative when tested with thyroid microsomal fractions which contained the organ-specific cellular antigens; where positive results were obtained there was clinical or serological evidence of thyroiditis. These sera were tested together against subcellular fractions prepared from the same liver. The results show that several antigens must be implicated in the A.I.C.F. reaction and that the antibody spectrum varies widely from one patient to another (cf. Deicher, Holman, and Kunkel, 1960).

Discussion

This study of systemic lupus erythematosus, rheumatoid arthritis, and thyroid auto-immune disease indicates that between these diseases there exists a degree of overlap of auto-antibodies greater than might be expected to occur by chance from control studies. Thus in our patients with S.L.E. the incidence of thyroid antibodies was approximately three times higher than in control subjects of the same age and sex. The antibodies were of low titre, and were detectable only by the sensitive tanned-cell test or, in the case of the second colloid antigen, CA2, by the fluorescent test. Although in this group C.F.T. results with homogenates of thyrotoxic glands were positive in 40% in high titre, reactions were almost invariably attributable to non-organ-specific antibodies, which reacted equally well with liver extracts but gave negative results with thyroid microsomal preparations. The five cases with combined disease (S.L.E. with Hashimoto's disease) gave the results expected—that is, antibodies specific for thyroid antigens, and antibodies typical of systemic lupus. In the rheumatoid arthritis group without goitre the incidence of thyroid antibodies was comparable to that found in controls. Three of the seven patients with goitre had low-titre antibodies corresponding with the incidence found in similar thyroid disease without R.A. Of the 79 R.A. patients without overt thyroiditis only two reacted in the C.F. test with thyroid microsomes, while seven sera gave A.I.C.F. reactions with human liver to titres of 1/16 or over. The incidence of this non-organ-specific reaction is thus much lower in R.A. patients than in the S.L.E. group. Buchanan *et al.* (1961) found thyroid complement-fixing antibodies in 12 of 46 female rheumatoid patients, whereas only three of their 73 cases had positive A.I.C.F. reactions. In female control cases these workers found thyroid C.F.T. in 11% as compared with the almost negative results of our tests for this group. This discrepancy may be partly explained by the greater sensitivity of the C.F. test used by Buchanan and co-workers in relation to serum concentration and amounts of complement. Yet, despite the greater sensitivity of their C.F. test, these workers find a lower incidence of A.I.C.F. in rheumatoid patients than was obtained in the present study. The possibility should therefore be considered that extracts of post-mortem adrenal, kidney, and liver used as antigen are not as sensitive as fresh thyroid gland for detecting the non-organ-specific A.I.C.F. reaction. In our opinion it is desirable to confirm the thyroid specificity of sera by testing them with thyroid microsomal antigen and also by demonstrating cytoplasmic fluorescence of thyroid cells with the Coons technique.

Our seven cases of combined R.A. and Hashimoto's disease were drawn from a series of over 300 Hashimoto sera tested, excluding cases of Sjögren's syndrome. This incidence is much lower than that reported by Beare (1958), who found three cases of R.A. among 27 cases of proved Hashimoto goitre in the London area. Buchanan *et al.* (1961) also found a higher incidence—five out of 31. We cannot at present explain the differences in incidence of the combined diseases found by us. It is possible that we were not always informed of other diseases present in patients sent to us for thyroid antibody tests. This seems unlikely, since the latex test for rheumatoid factor was performed on 98 of the Hashimoto sera and was found positive in only two.

It is noteworthy that in both the S.L.E. and uncomplicated R.A. groups the incidence of thyroid antibodies was confined to female patients, and that the occurrence of Hashimoto's disease in association with either S.L.E. or R.A. was found only in women. In contrast, the men in these two groups showed the same incidence as the women of A.I.C.F. reactions, A.N.F. and R.A. factor, and this suggests that thyroid antibodies might stem primarily from some abnormality in the thyroid itself rather than from an abnormal immunological reactivity in general.

In the great majority of *Hashimoto cases*, auto-immune phenomena were directed exclusively against the thyroid gland, and in the uncomplicated thyroiditis cases no L.E. cells were found. In a small proportion the spectrum of antibodies was wider, but reactions were of low titre, their incidence was little or no higher than in comparable control groups, and they were without apparent clinical significance.

The cases of thyroiditis combined with progressive hepatitis (Table III) showed coexistence of complement-fixing antibodies to both non-organ-specific antigens and the specific thyroid microsomal fraction.

The results reported here are in line with previous serological studies in human disease and in animal experiments, which suggest that auto-immune diseases involving body constituents might be broadly classified into two main categories (Mackay and Larkin, 1958; Asherson and Broberger, 1961). These could be designated "disturbed antigen" and "disturbed tolerance" diseases, exemplified on the one hand by Hashimoto's thyroiditis and on the other by systemic lupus erythematosus. In "disturbed antigen" diseases the relevant organ constituents are considered to be inaccessible to the lympho-reticular system and so fail to establish immunological tolerance in early life. Exposure of these substances to lymphoid elements after immunological maturity as a result of leakage from the tissue could evoke an immune response without implying marked abnormality of the R.E. system. This view is supported by the fact that these organ-specific antigens are able to evoke auto-antibody production in normal animals, as has been demonstrated with brain, testis, thyroid, adrenal, uveal tract, and lens constituents.

Furthermore, immunization with these materials often produces organ lesions in the injected animals resembling the parallel human disease (Waksman, 1959).

In contrast, the antigens characteristically involved in lupus erythematosus are widely distributed in body components, and, in the case of D.N.A.-protein for example, are even present in the antibody-forming cells themselves. Tolerance to them must therefore be presumed to exist in the normal state. These antigens fail to provoke auto-antibody production in experimental animals under conditions known to succeed with the organ-specific constituents, and lupus lesions have never been actively induced in animals. Burnet (1959, 1961) distinguishes between auto-immune diseases derived from defects of the antibody-forming cells and those depending upon some alteration in the distribution of normally inaccessible antigens. On the basis of his clonal selection theory he visualizes the emergence of forbidden clones arising by mutation and surviving by failure of an unknown homoeostatic mechanism to eliminate them. In the case of inaccessible antigens, the relevant clones are not eliminated in early life by the required contact with antigen.

Support for the concept that the underlying disturbances involve the antigen in one group of diseases and the antibody-forming system in the other is provided by family studies in the relatives of Hashimoto patients. Thus the high incidence of various thyroid disorders, such as colloid goitre and thyrotoxicosis as well as lymphadenoid goitre and primary myxoedema, suggests a constitutional abnormality of the thyroid gland, which seems to find expression in the greatly increased frequency of thyroid antibodies in these families (Hall *et al.*, 1960; Doniach *et al.*, 1961). In contrast, in the relatives of lupus patients there is a familial tendency to aberrations of γ-globulin synthesis such as hypergammaglobulinaemia (Leonhardt, 1959), and agammaglobulinaemia (Kunkel, 1959).

The differences and similarities between the two suggested categories of auto-immune diseases are summarized in Table V. While this division may provide a useful working hypothesis to approach the complex mechanism underlying the development of auto-immunity, it clearly represents an oversimplification. The two diseases lymphadenoid goitre and systemic lupus appear to be extreme examples at opposite ends of a spectrum of diseases showing varying immunological disturbances. Thus most other human diseases which have been linked with auto-immune phenomena, such as colitis (Broberger and Perlmann, 1959), pancreatitis (Thal, Murray, and Egner, 1959), progressive hepatitis (Mackay and Larkin, 1958), haemolytic anaemias (see Dacie, 1954), Sjögren's syndrome (Jones, 1958; Heaton, 1959; Bloch *et al.*, 1960; Bunim, 1961) and rheumatoid arthritis (see Glynn and Holborow, 1960), show a variable incidence of complex auto-antibody patterns, some of which are commonly found in S.L.E.

TABLE V.—*Comparison of Two Categories of Auto-immune Disease*

"Disturbed Antigen" Disease	"Disturbed Tolerance" Disease
Exemplified by Lymphadenoid Goitre	Exemplified by S.L.E.
Differences	
Antigen not normally circulating	Antigen accessible to lymphoid cells
Immune tolerance to antigens probably not established	Tolerance to antigens established in early life
Organ-specific antibodies produced in patient	Antibodies not necessarily organ-specific
Antibodies have narrow species-specificity	Antibodies have wide species-specificity
Narrow spectrum of antibodies produced	Often a wide variety of antibodies in patient's serum
Antigens capable of evoking antibody response in healthy animals	No antibodies produced in animals with comparable stimulation
Experimental lesions resemble human disease	Human disease difficult to reproduce in animals
Relatives of patient have tendency to several thyroid diseases	Relatives have disturbances of γ-globulin synthesis
Similarities	
Circulating auto-antibodies to normal body constituents	
Tendency to raised level of serum γ-globulin	
Lymphoid invasion of affected organs	
Variable damage to cells containing auto-antigens.	
Greater incidence in women.	
Disease process not always progressive (cf. discoid L.E. and focal thyroiditis)	
Circulating antibodies not primarily responsible for tissue damage (except presumably in haemolytic anaemia), but may act synergistically with "delayed type" hypersensitivity reactions	

These complex patterns include three classes of antibodies: those involving organ-specific antigens, A.I.C.F. reactions involving non-organ-specific cytoplasmic antigens, and the group of antinuclear factors. Antinuclear factors may reasonably be taken as a criterion of disturbed immunological tolerance. They are found in practically all cases of systemic lupus, in a high proportion of Sjögren cases, and to a lesser extent in other connective-tissue diseases. They have also been reported in progressive hepatitis, in hydrallazine syndrome, and in drug hypersensitivity; weak reactions occur occasionally in Hashimoto's disease. Nuclear antibodies have not yet been looked for in chronic pancreatitis, and we have tested for A.N.F. only five cases of adult ulcerative colitis, with negative results.

The A.I.C.F. reaction is not fully analysed with regard to the antigens involved. The group of antibodies reacting with various organ extracts is certainly very complex (Asherson, 1959), and some of the antigens may be organ-specific. It is not yet clear whether the A.I.C.F. reaction results from a defect in the antibody-forming system or whether "secluded" antigens common to a number of organs are released by cell injury. There is evidence for the latter possibility in the transient liver haemagglutinating or C.F. antibodies found in many patients after infective hepatitis (Haven, 1958), in cardiac infarction (Ehrenfeld *et al.*, 1961), and in rats following injections of carbon tetrachloride (Weir, 1961). It would be relevant to see if sera giving high A.I.C.F. titres in the absence of A.N.F. would react with leucocyte extracts, since the constituents of these cells presumably induce full tolerance in early life. In diseases of auto-immune pathogenesis where lesions are localized to one organ the cell destruction may be mediated primarily by the "delayed hypersensitivity" component of an immune reaction involving organ-specific antigens, and the non-specific A.I.C.F. antibodies may be a phenomenon secondary to this injury.

Sjögren's syndrome provides evidence for a combination of disturbed tolerance, as shown by the high incidence of antinuclear factors and of rheumatoid phenomena, together with an organ-specific destructive lesion in the salivary and lacrimal glands, though no specific antigens have yet been isolated from these organs. Curiously, these patients have a higher incidence and higher titres of thyroid-specific antibodies than are found in S.L.E. (Bloch *et al.*, 1960).

A disturbance of immunological tolerance could theoretically increase the likelihood of an immune response to organ-specific antigens, either by reducing the threshold of response to sporadic minute leakages from the relevant organ, or possibly by increasing such leakage through tissue damage resulting from inflam-

matory response to deposits of nuclear antigen-antibody complexes. The increased incidence of thyroid antibodies in the S.L.E. patients could arise in this way. The leakage theory may account for the antibody response to "secluded" antigens, but further as yet unknown factors must be sought to explain the sustained and progressive organ destruction so often observed in human auto-immune diseases. Progression of the lesions is not usually seen in the experimental auto-allergies induced in animals with organ-specific antigens in Freund adjuvants.

The mechanisms of immunological tolerance which prevent antibody formation against recognized self-constituents are still unknown, and several hypotheses have been discussed recently (for example, Asherson and Broberger, 1961). Where tolerance is already established it could break down either after some abnormality in the cells of the antibody-forming system, or because of modification of the antigens (? caused by mutations or virus and bacterial components). A small alteration in the metabolic degradation of a body constituent in the reticulo-endothelial system could expose new antigenic determinants. This may be one of the mechanisms by which Freund adjuvants enhance auto-antibody production in animals.

Our present ignorance of the basic mechanisms of immune tolerance and its breakdown in disease precludes the formulation of a well-defined theory of auto-immune diseases, but it is felt that the study of clinical and serological relationships in this group of disorders will increase our understanding of their development and progression and may ultimately shed some light on the disturbances which initiate them.

Summary

Patients with systemic lupus erythematosus, rheumatoid arthritis, and Hashimoto's disease, and with combinations of these conditions, were investigated for auto-antibody production. Tests were carried out for thyroid-specific antibodies, for the non-organ-specific antibodies giving the auto-immune complement-fixation (A.I.C.F.) test of Gajdusek, for L.E.-cell formation and antinuclear factors, and for rheumatoid factors (latex test). Thyroid antibodies were present in high titre in all the sera from the cases of Hashimoto's disease; in females with S.L.E. they were found, although in low titre only, with about three times the frequency observed in controls of comparable age and sex.

The incidence of thyroid antibodies in rheumatoid arthritis was confined to women, was not significantly higher than in the control group, and was similarly influenced by the presence of goitre.

The A.I.C.F. test was positive in 37% of the S.L.E. cases, in 10% of cases of rheumatoid arthritis, and in 5% of Hashimoto's disease. L.E. cell and A.N.F. tests were positive in all but one of the S.L.E. cases, and these two tests were positive, respectively, in 20% and 50% of the rheumatoid cases.

In Hashimoto's disease L.E. cell-tests were consistently negative and A.N.F. was seldom present, and then only in low titre. Latex tests were positive in 40% of S.L.E., and 55% of R.A. cases, and negative in Hashimoto's disease. The combination of Hashimoto's disease with S.L.E. or with rheumatoid arthritis was encountered only in women, and positive auto-antibody tests in these cases were distributed with frequencies approximately related to those found in each condition separately.

These findings are discussed. They appear to fit the concept that auto-immune diseases form, with some overlapping, a broad spectrum, at one end of which the immunological disturbance concerns mainly antigen, and at the other involves mainly antibody production.

We are grateful to the many colleagues who kindly sent us sera and clinical information about their patients. We thank Professor Kekwick and the Clinical Research Committee of the Middlesex Hospital Medical School for facilities afforded at the Institute of Clinical Research, and are pleased to acknowledge the skilled technical assistance of Miss H. R. E. Schuit and Mr. K. Couchman, F.I.M.L.T.

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5× Prednisone = Cortisone equivalent

TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH STEROIDS

REPORT TO THE MEDICAL RESEARCH COUNCIL BY THE COLLAGEN DISEASES AND HYPERSENSITIVITY PANEL*

The general conclusion of authors who have reported the results of treating many patients with systemic lupus erythematosus (S.L.E.) by steroid hormones (Haserick, 1953; Soffer, Elster, and Hamerman, 1954; Harvey, Schulman, Tumulty, Conley, and Schoenrich, 1954; Dubois, 1956) and also of those who have described smaller groups or single cases (May, 1953; Cohen and Cadman, 1953; Cosnett, 1954; Sylvester, 1954) is that these drugs have a beneficial suppressive effect on the disease. Improvement, however, is variable and unpredictable, and the incidence of dangerous complications is high, particularly in patients requiring large doses or prolonged treatment.

The uniformly bad prognosis of S.L.E. treated by other methods and the earlier reports on the value of steroids made a controlled trial ethically impossible, however desirable for scientific reasons. This survey of the results of treatment has therefore an inadequate background, and, like others, we have available for comparison only results of treatment in patients diagnosed before steroids became available.

The present study was designed to follow the progress of patients with S.L.E. treated with adequate doses of steroids. Patients, accepted into the series on satisfying specified diagnostic criteria, were drawn from teaching and non-teaching hospitals and from special units for the treatment of rheumatic diseases. Their progress was reported at three-monthly intervals on a standard form. In addition, a clinical summary covering the period was requested. Further information required when the results were studied was obtained where necessary from a perusal of the original hospital case notes.

Material and Methods

Selection of Cases

The following criteria were laid down for admission to the series:

A. *Obligatory:* An erythrocyte sedimentation rate (E.S.R.) of 20 mm. or more in the first hour, estimated by the Wintrobe or Westergren method.

B. *Major Criteria:* (1) A rash compatible with S.L.E. (2) Leucopenia, defined as a white-cell count below 5,000/c.mm. (3) The demonstration of the L.E. factor in the patient's serum.

C. *Minor Criteria:* (1) Arthralgia or joint effusions. (2) Serositis. (3) Fever above 99° F. (37.2° C.) twice in 24 hours. (4) Retinal changes. (5) Differential agglutination titre (D.A.T.) of 1/16 or over. (6) Proteinuria.

To qualify for entry to the series a patient must have fulfilled the obligatory criterion plus two or more major criteria, or the obligatory criterion plus one major and at least two minor criteria. These criteria were adopted on the basis of an analysis of 55 cases of S.L.E. studied by E. G. L. Bywaters and W. Bauer (1939, not published), the personal experience of members of the Collagen Diseases Panel, and a study of the literature.

*Members of the Panel: Professor Sir George Pickering (chairman), Professor E. G. L. Bywaters, Professor J. F. Danielli, Dr. P. G. Gell, Professor J. H. Kellgren, Dr. D. A. Long, Dr. A. Neuberger, Dr. H. Nicholson, Professor F. T. G. Prunty, Dr. A. H. T. Robb-Smith, Professor G. Payling Wright, Dr. E. T. Conybeare, and Dr. J. J. R. Duthie (secretary).

In all, 113 patients were accepted for study. Six were withdrawn in the early weeks. Of these, three refused to co-operate, one left the country, one died before treatment began, and one was withdrawn by her physician. All the patients still alive have completed at least two years from the start of treatment.

Method of Treatment

It was recommended that all patients should be treated with oral cortisone. The dosage suggested was 300 mg. on the first day, 200 mg. on the second day, and 100 mg. a day for the rest of the first week. Thereafter the dose was to be adjusted to suppress all symptoms and signs of the disease without, if possible, producing undesirable side-effects. In patients failing to respond to cortisone, corticotrophin (A.C.T.H.) might be given a trial, but a return to cortisone was recommended if the disease came under control. It was requested that in the treatment of infections the use of sulphonamides be avoided, but adjuvant therapy might include antibiotics, low-sodium diet, diuretics, and supplementary potassium if indicated.

Characteristics of the Group

The frequency with which the various diagnostic criteria were satisfied is shown in Table I. It might appear from this table that in addition to renal involvement, which is known to be a serious complication,

TABLE I.—*Numbers of Patients Fulfilling Diagnostic Criteria*

Criteria	Patients Alive at 2-year Follow-up of Whole Group	No. of Deaths	Total
Fever	54	40	94
Arthralgia	59	39	98
Rash	42	39	81
Serositis	22	15	37
*Retinitis	7	12	19
*Leucopenia	30	35	65
*Proteinuria	11	32	43
L.E. cells	50	44	94
D.A.T. 1/16 or over	14 out of 24 reported	11 out of 19 reported	23 out of 43 reported
Total	61	46	107

*P<0·02.

leucopenia indicates a poor prognosis (P<0.02). However, of the 35 patients with leucopenia who died, 27 also had proteinuria, and it is probable that the renal lesion was the significant factor.

Comparison of this group with others recorded in the literature (Shearn and Pirofsky, 1952; Jessar, Lamont-Havers, and Ragan, 1953; Harvey *et al.*, 1954; Dubois, 1956) shows a similar incidence of joint symptoms, fever, rash, and the L.E. cell phenomenon. In the present series involvement of serous membranes and kidneys is less common than in these authors' cases, perhaps because the incidence of the manifestations in the present series is based on findings at entry to the study.

Although the detailed examination of the necropsy material from 31 of the 46 fatal cases has not yet been reported, it may be said, with reference to the usefulness of the diagnostic criteria, that in only two cases was definite evidence of S.L.E. not found on microscopical examination of tissues. One patient had had "rheumatic fever" in 1927, and it is possible, although L.E. cells were reported, that she died in heart failure as a result of a recurrence of this disease. The second histologically doubtful patient had long-standing "rheumatoid arthritis" with a positive L.E. cell preparation in life.

Age and Sex Incidence on Entry to Series.—The well-known predominance of females and young people is shown in Table II, and corresponds with all other series published.

TABLE II.—*Age and Sex Incidence on Entry to Series*

Age	Female	Male	Total
Less than 10 years ..	0	1	1
10–19 years	12	3	15
20–29 ,, ...	21	1	22
30–39 ,, ...	23	2	25
40–49 ,, ...	20	3	23
50–59 ,, ...	9	2	11
60–69 ,, ...	7	0	7
70–79 ,, ...	2	0	2
80+ ,, ...	1	0	1
Total ..	95	12	107

Probable Duration of Disease.—An attempt has been made to assess the length of history up to the time of entry to the study by recording what may reasonably have been the earliest feature of the disease (Table III). In the majority (72 out of 107) the duration of symptoms was less than three years, and the general form of the age incidence shown in Table II will not be altered if this is taken into account. It is to be noted that at all durations joint symptoms account for about half the presenting symptoms.

Results of Treatment

Mortality Rate

Two years after the last patient had been accepted into the series there were 67 survivors, 6 of whom were in their sixth year of treatment. In patients living longer than two years only six further deaths were reported. The highest mortality occurred in the first six months among patients severely ill with renal involvement. The death rate among patients at risk at intervals is shown in Table IV. The 40 patients dying in the first two years of the trial had a mean survival time from entry to death of 8.5 months. They had, estimated by the method used to compile Table III, a mean past history of 34.3 months, making a mean survival time from probable onset to death of 42.8 months. Dubois (1956) found that 33 patients who died and who were "adequately treated" had a mean survival time from onset of 62.5 months. Comparison is unsatisfactory because Dubois often used much larger doses of hormone to suppress symptoms. In 12 patients who were resistant he used doses "as large as 4,000 mg. per day for six weeks." None of the present group was given doses approaching this level even when the disease was out of control (see Table IX).

Harvey *et al.* (1954) found that 18 out of their 62 steroid-treated patients died in just over four years, but 24 of these had been on treatment less than two years before the report. These authors varied their methods of administering the drugs, but, basically, their patients received as short a course of steroid as possible, the dose being reduced and being stopped as soon as the disease became quiescent "or the manifestations were of a minor nature." As stated above, in the present group treatment was initially directed at suppressing all features of the disease. These different methods employed in the use of hormones are a further source of confusion in assessing the overall efficacy of these drugs.

There is no adequate series of untreated cases for comparison, but of the group of cases studied by Bywaters and Bauer (1939, not published), 29 (52.3%) were dead two years after onset of the disease. In the present group 17 out of the 107 (15.9%) were dead two years after onset, and 40 out of 107 (39%) two years after the start of treatment. Although the diagnostic criteria were similar (apart from the L.E. cell phenomenon and the D.A.T.) these groups are not directly comparable, and, indeed, other factors probably played a major part in the longer survival of the treated group. Among these factors are the use of antibiotics, blood transfusions, and improved knowledge of electrolyte problems and renal failure.

Dubois (1956) used as a control group 34 cases treated by antibiotics alone. In these the mean duration of the disease was 38.5 months compared with 62.5 months in "adequately treated" patients who received steroid with or without antimalarial drugs.

TABLE IV.—*Death Rate in Patients at Risk.* (*Deaths Numbered* 46)

Period from Date of Entry (Months)	No. of Patients Exposed to Risk of Dying	No. of Patients Not Completing Period	Deaths	Death Rate (%)
0– 3	107	—	14	13·1
3– 6	93	—	10	10·7
6–12	83	—	4	4·8
12–18	79	—	7	8·9
18–24	72	—	5	6·9
24–36	67	10	5	
36–48	52	45	1	
48–60	16	55	0	
60–72	6	61	0	

Renal Involvement and its Effect on Prognosis

All but 7 of the 46 patients who died had evidence of a renal lesion, and the majority were in some degree of kidney failure at the time of death. The level of proteinuria was not altered by treatment in any of the patients who died. Table V shows the cause of death in the seven patients who had no renal involvement which was demonstrable in life. Dubois (1956), on the

TABLE III.—*Probable Duration of Disease Before Entry*

Initial Symptom	Duration of Symptom before Entry												Total
	Months			Years									
	3	3–6	6–12	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9+	
Serositis	—	2	1	—	3	—	1	—	—	—	1	—	8
Rash	4	4	4	4	2	1	1	1	—	—	2	7	30
Dyspnoea	—	—	1	1	—	1	—	—	—	—	—	—	3
Fever	—	—	—	1	—	—	—	—	—	—	—	—	1
Weight loss	1	—	—	1	—	—	—	—	—	—	—	—	2
Arthralgia	9	7	7	7	7	4	4	2	2	—	—	5	54
Malaise	1	1	—	2	—	—	2	—	—	—	—	—	6
Proteinuria	—	1	—	—	1	—	—	—	—	—	—	—	2
Raynaud's phenomenon ..	—	—	—	—	—	—	—	1	—	—	—	—	1
Total ..	15	15	13	16	13	6	8	4	2	0	3	12	107

TABLE V.—*Cause of Death in Seven Patients Without Evidence of Renal Involvement During Life*

Patient	Age	Cause of Death	Survival Time	Histology
O.C.	54	Skin ulcers: cachexia	2 months	Kidneys normal
V.A.	42	Mitral stenosis	6 ,,	Cardiac failure
M.H.	50	Bronchopneumonia	26 ,,	Normal kidneys
K.T.	52	Cerebrovascular accident	3½ ,,	No necropsy
W.W.	39	Lung involvement	6 ,,	Normal kidneys
W.Y.	16	Convulsions	8 ,,	Renal lesions
A.D.	42	Appendicitis	13 ,,	Kidneys normal

other hand, found progressive lesions in the central nervous system to be as common a cause of death as kidney failure.

At the two-year follow-up of the whole group, 11 patients who had any evidence of renal involvement at the start of treatment were still alive. Some aspects of their progress are summarized in Table VI. In two patients the proteinuria cleared spontaneously and in three (V.J., W.N., and B.G.) it was not affected by

TABLE VI.—*Summary of 11 Patients, Still Alive at Two-year Follow-up, With Renal Lesions at Start of Treatment*

Patient	Duration of Proteinuria on Treatment	On Steroid at Time of Remission	Survival Time	Comment
J.B.	3 weeks	Yes	5 years	Disease inactive
C.C.	36 ,,	,,	3 ,,	,, active
B.C.	26 months	No	4 ,,	Off steroids for 2 years
S.E.	5 weeks	Yes	4 ,,	Relapse when cortisone stopped
E.F.	6 ,,	,,	5 ,,	Well. B.P. 160/110
V.J.	Still present	—	3 ,,	
M.M.	12 months	No	3½ ,,	E.S.R. less than 20 for 3 years
W.N.	Still present	—	3 ,,	Proteinuria still 200–700 mg./100 ml.
D.S.	6 months	Yes	4 ,,	B.P. rises on steroids
W.T.	2½ years	,,	4½ ,,	E.S.R. less than 20 for 2½ years
B.G.	Still present	—	3 ,,	B.P. 175/125

steroids, although all three were alive three years after start of treatment. In the remaining six patients the improvement may possibly have been due to the hormone, but the abolition of fever may itself be accompanied by decreased proteinuria.

Effect of Treatment on Other Manifestations

The frequency of fever, arthralgia, L.E. rash, and serositis in the group at intervals is shown in Table VII. From this table it would appear that arthralgia and rash are more resistant to treatment than the fever or

TABLE VII.—*Frequency of Fever, Arthralgia, L.E. Rash, and Serositis at Intervals From Start of Therapy*

Symptom	On Entry to Group	Months					
		3	6	12	24	36	48
Fever	54	16	6	7	4	1	0
Arthralgia	59	34	33	30	23	11	4
L.E. rash	42	31	29	25	18	16	2
Serositis	22	19	15	16	7	6	2
No. of patients at risk	107	93	83	79	67	52	16

serous inflammation. Harvey *et al.* (1954) found that in patients with long-standing joint swelling or deformity the pain was but slowly relieved. In the present group there were 11 patients who had had a chronic deforming arthritis for over three years before the diagnosis of S.L.E. was made, and it may be that in these cases the joint pains were not always those of active arthritis. Similarly, the apparent relative failure of the rash to respond may have been due in part to the presence in the group of 12 patients who had "chronic discoid L.E." for over three years before involvement of other systems and start of steroid treatment. Even allowing for these perhaps artificial subdivisions, between a fifth and a quarter of patients alive at the selected intervals had a rash or joint pains.

In those patients whose temperature fell on starting treatment, the fall occurred in the first 24 to 72 hours. This was also noted by Soffer and Bader (1952) and Harvey *et al.* (1954). In Harvey's patients, 50 of whom were febrile at the start of steroid treatment, 35 again developed a pyrexia during or shortly after the initial course. Sixteen of the present group were febrile three months after commencing treatment.

Effect of Treatment on the E.S.R.

Table VIII shows the general improvement in the E.S.R. after starting treatment. A more detailed analysis of this is given in Table IX, where the sedimentation rate is correlated with the average daily dose of cortisone over the preceding three months. This table shows no obvious direct relationship between

TABLE VIII.—*E.S.R. at Intervals After Start of Treatment*

E.S.R. (mm. in 1st hour)	On Entry	Months						
		3	6	12	24	36	48	60
–20	0	23	27	19	20	20	7	2
21–30	12	9	17	12	10	9	3	1
31–40	9	17	6	12	7	7	2	1
41–50	14	7	7	6	3	7	1	0
51–60	16	6	5	5	4	0	1	1
61–70	12	7	2	1	1	1	0	0
71–80	10	7	4	3	2	0	0	0
Over 80	34	7	5	7	1	0	0	0
Not known	0	10	10	14	19	8	2	1
Dead	0	14	24	28	40	45	46	46

TABLE IX.—*Correlation of E.S.R. With Average Daily Dose*

Dose of Cortisone (mg.) Daily	E.S.R.	Months						
		3	6	12	24	36	48	60
0	<20	0	2	3	4	4	1	0
	20–50	2	1	1	1	2	1	0
	>50	3	0	4	2	1	0	0
<50	<20	4	4	2	5	1	1	0
	20–50	0	3	1	1	2	1	0
	>50	2	2	0	0	0	0	0
50–99	<20	8	13	8	3	10	3	1
	20–50	13	14	14	12	11	4	1
	>50	10	10	6	5	0	1	1
100–149	<20	8	6	4	6	4	1	2
	20–50	15	11	13	4	5	0	0
	>50	9	4	6	1	0	0	0
150+	<20	3	2	2	2	1	1	0
	20–50	3	1	1	2	3	0	0
	>50	3	0	0	0	0	0	0

the doses used and the E.S.R. at the chosen time intervals. It will be seen that the majority received between 50 and 150 mg. of cortisone daily. The figures suggest that if a normal E.S.R. were the sole criterion of satisfactory treatment larger doses might have been employed. However, the risks of incapacitating side-effects rise steeply when doses larger than the maximum quoted are given, and most physicians would prefer a compromise between disease activity and iatrogenic disability.

Twenty-one cases were treated with the delta analogues of cortisone and hydrocortisone as they became available (prednisone 13, prednisolone 8). In Table IX the doses of the delta analogues have been multiplied by five and expressed as "cortisone." It may be said here that the change from cortisone to prednisone (or prednisolone) was not followed by any noticeable or haematological change in 20 of these patients. The remaining patient, who had developed mild Cushing's syndrome, benefited from the change,

not by an improvement in the control of the disease but by a loss of 10 lb. (4.5 kg.) in weight in the first month.

Bollet, Segal, and Bunim (1955) agree that the effectiveness and limitations of prednisone and prednisolone are similar to those of cortisone and A.C.T.H., apart from the abolition of salt-and-water retention. Using methylprednisolone and dexamethasone, Dubois (1959, 1960) came to similar conclusions.

Effect of Treatment on the Functional State

Over and above the response of the individual manifestations of disease activity already considered, the general state of the patient and his or her ability to lead a useful life were assessed. Three grades of "functional state" (F.S.) were adopted for this purpose.

1. Well; leading normal life with no incapacity.

2. Some symptoms; restricted activity but able to do most housework or part-time or light work.

3. Severely handicapped; unable to work, confined to house or bedridden, requiring help with toilet or dressing.

It was felt that to adopt a larger number of F.S. groups would lead to confusion in the analysis as so many physicians with individual interpretations were participating in the study. Table X shows the general improvement in the majority of the survivors at intervals.

On entry only 10 of the 107 were in F.S.1. At the end of the first year 34 of 79, and at the end of the second year 32 of 67, were in F.S.1. After the manner adopted to compile Table IX, the dosage was related to the F.S.1 at the same intervals, and there was no evidence that those on larger doses were more or less incapacitated by disease (or drug intoxication) than those on small amounts. Comparison of Tables VIII and X shows that, in the first six months at least, the E.S.R. and F.S. equally reflected disease activity. Thereafter the E.S.R. appears to have been less well

TABLE X.—*Functional States at Intervals in Survivors*

Functional State	On Entry	Months						
		3	6	12	24	36	48	60
1	10	19	27	34	32	30	10	0
2	28	46	41	30	28	17	6	4
3	69	28	15	15	7	5	0	2
Dead	0	14	24	28	40	45	46	46

controlled than the patients' general state. This might suggest that in patients treated for many months the physicians were more concerned with maintenance of general well-being and usefulness than in strict suppression of disease activity, preferring to avoid or minimize side-effects of treatment.

Complications of Steroid Therapy

Many of the known side-effects of steroid therapy resemble the manifestations of S.L.E., and differentiation of the two is often impossible. Table XI shows the incidence of some of the probable hormone-induced symptoms. A raised blood-pressure is perhaps one of the findings most difficult of assessment in this respect. In this report hypertension has been defined as a systolic pressure of 30 mm. Hg or more or a diastolic pressure of 20 mm. Hg or more above the level expected for age and sex (Hamilton, Pickering, Fraser Roberts, and Sowry, 1954). In addition the hypertension was not considered to be a direct result of therapy if (1) evidence of a renal lesion antedated the rise in blood-pressure, and (2) if the blood-pressure did not fall within two weeks of any reduction of the steroid dose. These criteria will certainly exclude some cases of hormone-induced hypertension. Although in most instances this complication developed in the first year of treatment, hypertension was still appearing for the first time in the fourth year of therapy. It will be noted from Table XII that the actual dose did not appear to be related to the rise in blood-pressure.

TABLE XI.—*Complications of Steroid Therapy*

Complication	Months						Total
	0–3	3–6	6–12	12–24	24–36	36–48	
Hypertension	3	4	3	3	1	2	16
Crush fracture of vertebra	1	—	—	—	1	—	2
Gut haemorrhage	—	1	1	—	2	—	4
Infection	1	—	2*	1	1	—	5
Psychotic changes	5	1	—	3	—	—	9
Dyspepsia	1†	1	—	—	—	—	2
Glycosuria	—	1‡	—	—	—	—	1
Hirsutism	2	—	—	—	—	—	2

* One case of pulmonary tuberculosis treated with isoniazid and P.A.S. Steroid therapy continued throughout. Now off all drugs.
† Radiologically proved gastric ulcer. Steroid discontinued. Patient died a year later of appendicitis. No necropsy.
‡ Glucose-tolerance curve not available.

TABLE XII.—*Hormone-induced Hypertension Related to Dose*

	Interval in Months from Start of Therapy					
	0–3	3–6	6–12	12–24	24–36	36–48
Individual doses at which rise in B.P. occurred (daily dose in mg.)	75 87·5 75	100 400 100 200	75 75 100	110 112·5 100	32·5	50 100

Soffer *et al.* (1954) stated that hypertension occurred in more than half their patients (18 out of 32), but they do not define hypertension, nor do they attempt to differentiate between that produced by disease and that by steroid. Harvey *et al.* (1954) found the total incidence of high blood-pressure to be 17 out of 62 patients treated with steroid. This is more in accordance with the findings in the present series.

In considering "infections" in Table XI minor conditions such as boils, styes, paronychia, and acne have not been included, and only more serious illnesses have been considered (pneumonia, septicaemia, renal-tract infections, and tuberculosis). No cases of meningitis occurred. Empyema thoracis did not follow any of the pleuritic symptoms of the disease. Peritonitis occurred once as a complication of the appendicitis from which the patient died (A.D., see Table V).

The psychiatric complications, which are among the most distressing manifestations of steroid intoxication, fell broadly into two groups: (1) depressive states with paranoid delusions, and (2) confusional states with or without hypomania. The mild euphoria so often associated with steroid therapy has been disregarded. Six patients showed moderate psychiatric manifestations which resolved without specific psychiatric treatment or change in the dose of hormone. Three patients, one terminally, were committed to mental hospitals.

The cases of the two patients who were still alive at the time of writing are described below.

W.R.—A woman aged 23 was incapacitated by polyarthritis at the start of treatment. This and a rash and retinitis cleared within the first few months of treatment and her E.S.R. fell to normal. She remained well for two years on 200 mg. of cortisone daily. Then a relapse of the arthritis and a rise in the E.S.R. led to the dose being increased to 300 mg. daily. She became paranoid, deluded,

and depressed, and attempted suicide. She was transferred to a mental hospital, where the dose was slowly reduced to 50 mg. daily with improvement of her mental state to normal and no relapse of her other symptoms.

G.F.—A girl aged 18 had severe arthritis, lymphadenopathy, rash, and dyspnoea at the time of diagnosis. The disease was slowly controlled over six months and she was discharged on 75 mg. of cortisone daily. The E.S.R. remained high. Six months later she was readmitted to hospital with pyrexia, rash, and active arthritis. In addition, she was agitated, confused, and disorientated. The steroid was reduced and salicylate added to control her joint pains and temperature. Her mental condition worsened and she became hallucinated and was transferred to a psychiatric hospital. The cortisone was gradually discontinued, and over the course of two months her psychotic disturbance cleared completely without relapse of the other symptoms.

Although in both these cases improvement followed reduction or cessation of the hormone therapy, the relationship is complicated by the appearance of the psychiatric illness during a relapse of the disease itself, albeit with an increase in the dose in the first case. Harvey *et al.* (1954) in their group had nine patients who became psychotic while on steroid, but these authors do not comment on the disease activity at the time. Soffer *et al.* (1954), accepting euphoria as a psychiatric complication, found "some form of mental aberration" in two-thirds of their cases. They, too, noted that depression and paranoia were common. Ziff, Esserman, and McEwen (1958) were of the opinion that psychiatric symptoms were due to the disease itself and could be controlled by increasing steroid dosage. Thus in any one case it is difficult to know whether to increase or decrease dosage. As lowering the dosage is slow, it may be thought better to try a rapid increase first and then, if there is no response, a fairly rapid initial decrease to previous levels before tapering.

Discussion

In a lethal disease that is subject to spontaneous remissions of varying frequency, length, and degree over a period of many years the value of any therapeutic agent is difficult to assess. The steroid hormones produce side-effects which in a proportion of cases may be more disabling than S.L.E. itself and in some instances fatal. The variability with which patients respond to therapy makes adequate management a matter of trial and error in the majority.

It is generally accepted that steroids relieve the symptoms and lessen disease activity in S.L.E. This is borne out by the present study, which represents an analysis of the experience of many physicians, of the disease and its treatment. The effect of the hormone in acutely ill patients with florid symptoms was usually rapid and dramatic, except in respect of the important renal lesion. The initial improvement was maintained to a greater or less degree. The response to a subsequent reduction of the dose varied in individual patients, some of whom relapsed severely while others remained well. However, the dosage was not as high as that used by Dubois (1956) and not as high (47 mg. of prednisone a day) as that claimed by Pollak, Pirani, Muehrcke, and Kark (1959) to prevent the development of renal failure.

It is suggested that at the present time steroids should be used in all patients severely ill with S.L.E. Much larger doses than those employed in the present study might be used for severe exacerbations, since failure to control a florid relapse is probably more dangerous than the risk of using massive doses over a short period.

Patients with less active disease should be maintained for as long as possible on salicylates, with or without antimalarial drugs, but the majority will eventually require steroids over varying lengths of time. As noted above, confirmation of the claim to obviate renal damage by high doses of prednisone is urgently needed, since this is the major cause of death nowadays. In those patients without renal disease of any sort the dose of steroid should be kept to a minimum, the therapeutic regimen being designed to maintain the optimal functional state without serious side-effects in each case. The E.S.R. in the present group did not appear to reflect the clinical state with any degree of accuracy. To insist on maintaining the E.S.R. at normal levels is to run the risk of hormone intoxication without any guarantee of a practical therapeutic advantage. There is no definite evidence that prolongation of life is more likely to be achieved by complete suppression of all signs of activity than by control of symptoms only. Dubois (1960) also found the E.S.R. an unreliable guide to the patient's clinical state in this respect.

With regard to the form of hormone used, it was noted in this study that cortisone and hydrocortisone were equally potent in comparable doses with their delta analogues, though when salt-and-water retention is a problem the latter are to be preferred.

Summary

The results of treatment with steroid hormones of 107 patients suffering from systemic lupus erythematosus over a minimum period of two years are described and compared with those reported by other authors.

The majority of symptoms are rapidly though not permanently relieved, but the effect on the mortality rate is uncertain in the absence of a control group. There is no doubt, however, that in individual patients the drugs are temporarily life-saving.

The incidence of side-effects was felt to be remarkably low, and it is suggested that larger doses of steroid than those administered to this group of patients may be given for a longer time in patients not responding to treatment. There appeared to be no therapeutic advantages in using any one form of steroid hormone, but electrolytic disturbances will be less of a problem if the delta analogues are used.

The E.S.R. has not been found to reflect accurately the clinical state of the patient, and it is regarded as unwise to insist on maintaining a normal sedimentation rate using larger doses than are needed to keep the patient symptom-free.

At the present time, in the absence of a superior therapeutic agent, it seems imperative that patients ill with systemic lupus erythematosus should be treated vigorously with steroid hormones.

The Panel is greatly indebted to its secretary, Dr. J. J. R. Duthie, for his labour and tact in keeping this trial in progress, to Dr. G. S. Wakefield for compiling the data contained in this report, and to the physicians who gave of their time and interest to keep the records which made the trial possible.

The following hospitals co-operated in the trial: Bedford General Hospital; Birmingham General Hospital; Canadian Red Cross Memorial Hospital, Taplow; Croydon General Hospital; Gorleston Hospital, Norfolk; Hammersmith Hospital; Llandough Hospital, Cardiff; London Hospital; Maelor General Hospital, Wrexham; Mayday Hospital, Thornton Health; Minffordd Hospital, Bangor; Norfolk

and Norwich Hospital; Northampton General Hospital; Northern General Hospital, Edinburgh; Orpington Hospital; Princess Louise Hospital; Queen Elizabeth Hospital, Birmingham; Queen Mary's Hospital, Sidcup; Radcliffe Infirmary, Oxford; Redhill County Hospital, Surrey; Royal Alexandra Hospital, Rhyl; Royal Infirmary, Cardiff; Royal Infirmary, Manchester; Royal National Hospital for Rheumatic Diseases, Bath; Royal Sussex County Hospital, Brighton; St. Alfege's Hospital, Lewisham; St. Asaph Hospital, Flints; St. David's Hospital, Cardiff; St. Martin's Hospital, Bath; St. Mary's Hospital, Paddington; St. Thomas's Hospital, London; University College Hospital, London; Western General Hospital, Edinburgh; Westminster Hospital, London; Willesden General Hospital, London.

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HYPOGAMMAGLOBULINAEMIA IN CHRONIC LYMPHATIC LEUKAEMIA

BY

G. HAMILTON FAIRLEY, M.A., D.M., M.R.C.P.
Leverhulme Research Scholar, Royal College of Physicians of London

AND

RONALD BODLEY SCOTT, M.A., D.M., F.R.C.P.
Physician, St. Bartholomew's Hospital, London

It has been known for nearly fifty years that patients with chronic lymphatic leukaemia may be incapable of forming antibodies against *Salmonella typhi* either in response to infection or after inoculation with typhoid vaccine (Moreschi, 1914; Howell, 1920). This immunological inadequacy is now fully documented (Bernstein, 1934; Weinstein and Fitz-Hugh, 1935; Larson and Tomlinson, 1953; Shaw *et al.*, 1960; Barr and Fairley, 1961); it differs, moreover, from that observed in certain other malignant diseases of lymphoreticular tissue such as Hodgkin's disease, acute leukaemia, and chronic myeloid leukaemia. In these disorders the ability to form antibodies on primary immunization is impaired, but on re-immunization is normal or but slightly defective; in chronic lymphatic leukaemia the antibody response both to primary immunization and to re-immunization is depressed (Barr and Fairley, 1961).

The impaired formation of circulating antibodies in chronic lymphatic leukaemia is often accompanied by an abnormal gamma-globulin content of the serum. Reduced levels, or even absence, have been recorded (Brown *et al.*, 1948; Brem and Morton, 1955; Jim and Reinhard, 1956; Wall *et al.*, 1956; Jim, 1957; Sunderman and Sunderman, 1957; Creyssel *et al.*, 1958; Prasad, 1958; Teitelbaum *et al.*, 1959; Ultmann *et al.*, 1959; Hudson and Wilson, 1960; Onat and Cooper, 1960; Shaw *et al.*, 1960; Videbaek, 1960). In five of the largest series the frequency of hypogammaglobulinaemia has been variously reported as 19% of 47 (Videbaek, 1960), 36% of 50 (Jim, 1957), 50% of 61 (Creyssel *et al.*, 1958), 64% of 36 (Shaw *et al.*, 1960), and 68% of 40 (Hudson and Wilson, 1960). These discrepancies are partly explained by the different criteria of normality accepted by different observers.

Other authors record an increase in the gamma-globulin concentration of the serum (Neely and Neill, 1956). In one series this was noted in 24% of 50 patients (Jim, 1957), although Creyssel *et al.* (1958) believe it to be of rare occurrence and Hudson and Wilson (1960) met it in none of their 40 patients. In the majority of such cases paper electrophoresis shows a diffuse increase in the gamma-globulin fraction, but there have been reports of abnormal localized bands similar to those found in myelomatosis (Rundles *et al.*, 1954; Teitelbaum *et al.*, 1959). These could be explained by an excess of macroglobulin, for ultracentrifugation was not undertaken and the association of chronic lymphatic leukaemia and macroglobulinaemia has been noted in a few instances (Mackay *et al.*, 1957; Glenchur *et al.*, 1958; Braunsteiner and Sailer, 1960).

The frequency of infection in chronic lymphatic leukaemia has long been recognized and the suggestion is often made that it is related to the hypogammaglobulinaemia and the inability to form circulating antibodies (Wintrobe and Hasenbush, 1939; Osgood and Seaman, 1952; Hougie, 1956; Scott, 1957; Dameshek and Gunz, 1958; Reinhard *et al.*, 1959). This paper reports estimations of the quantity of gamma-globulin in the sera of 110 patients with this disease; it attempts to relate to it the frequency of bacterial infection and it describes the prophylactic use of gamma-globulin in cases of hypogammaglobulinaemia.

Selection of Cases

The gamma-globulin concentration was estimated in the sera of 110 patients with chronic lymphatic leukaemia and of 55 controls.

A diagnosis of chronic lymphatic leukaemia was accepted only when the peripheral lymphocyte count before treatment was constantly above 9,000/c.mm. or when the bone-marrow contained more than 40% of lymphocytes. These figures exceed by 100% the upper limits of normal (Osgood *et al.*, 1939; Scott, 1939; Dacie, 1956): by adopting such criteria some cases of chronic lymphatic leukaemia may have been overlooked, but none will have been wrongly included.

The controls were chiefly healthy blood donors, although some patients, convalescent from fractures but otherwise well, were included to widen the range of ages.

Methods

Gamma-globulin estimations were made by two methods.

Paper Electrophoresis (Flynn and de Mayo, 1951).—0.02 ml. of serum was applied to a strip of Whatman

No. 1 paper 7.5 cm. wide and the separation performed in barbiturate buffer (*p*H 8.6 ; ionic strength 0.05) for 16 hours at 2.5 volts per cm. length of strip. The strips were dried for 20 minutes at 100° C., stained with light green, and washed repeatedly in 2% acetic acid until a white background was obtained. After drying, the strips were made translucent by immersion in oil (Grassmann *et al.*, 1951) and passed through an electrodensitometer (Laurence, 1954) to obtain a tracing of the protein pattern. The relative concentration of each fraction was obtained by measuring the area under each curve by planimetry and the absolute values calculated from the total protein concentration determined by the biuret method (Gornall *et al.*, 1949). The normal range of gamma-globulin obtained by this technique was 1.10–1.75 g./100 ml. of serum with a mean of 1.38 g. (Fig. 2). This is similar to the results of other workers using the same method (Gilliland *et al.*, 1956 ; Sunderman and Sunderman, 1957).

Immunological Techniques. — (*a*) Agar diffusion method: This was carried out by Dr. J. F. Soothill using the technique of Gell (1957). (*b*) Gamma-globulin neutralization method: The technique used was that described by Mollison (1956), and depends upon the neutralization by human gamma-globulin of the reaction between Rh-positive sensitized red cells and anti-human globulin serum. The anti-human globulin serum used for this test was supplied by Dr. A. E. Mourant from the Blood Group Reference Laboratory.

These two methods give similar results. The normal range is 0.80–1.20 g. of gamma-globulin per 100 ml. of serum, with a mean of 1.00 g.

Results

Four basic gamma-globulin patterns were found on electrophoresis of the sera from the 110 patients with chronic lymphatic leukaemia. In 29% the level was within the normal range, in 67% it was reduced, in 3% it was raised without an excess of macroglobulin, and in 1% (one patient) there was macroglobulinaemia (Fig. 1).

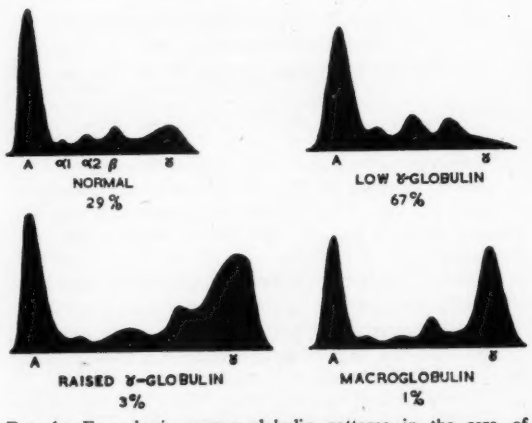

FIG. 1.—Four basic gamma-globulin patterns in the sera of 110 patients with chronic lymphatic leukaemia, showing the percentage with each pattern.

The distribution of the gamma-globulin levels determined by electrophoresis in these patients is shown in Fig. 2. In 12% the figure was below 0.5 g./100 ml. ; in the three patients with a raised concentration, but no excess of macroglobulin, the levels were 1.84, 2.33, and 3.55 g./100 ml. ; and for the single patient with macroglobulinaemia 3.75 g. In this case ultracentrifugal analysis, carried out by Professor N. H. Martin, showed an excess of macroglobulin with a sedimentation constant of S_{20w}19.5 (Fig. 3).

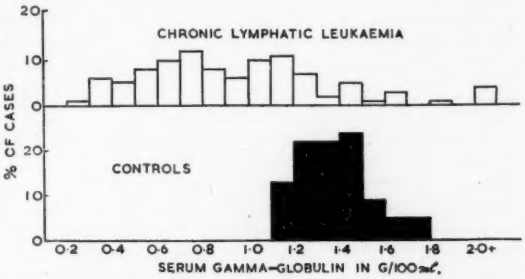

FIG. 2.—Serum gamma-globulin concentrations in 110 patients with chronic lymphatic leukaemia compared with those in 55 controls.

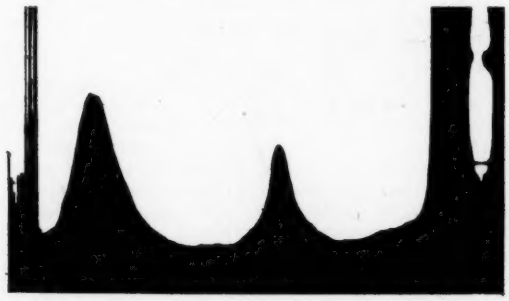

FIG. 3.—Ultracentrifugal analysis of serum from man aged 49 with chronic lymphatic leukaemia, showing excess of macroglobulin with a sedimentation constant of S_{20w}19.5.

Clinical Significance of Hypogammaglobulinaemia

The importance of hypogammaglobulinaemia lies in its frequent association with troublesome and recurrent bacterial infection. Fig. 4 shows the number of proved infective episodes occurring in each patient during the past year compared with the serum gamma-globulin concentration determined by paper electrophoresis. In all who suffered more than three infections in the year

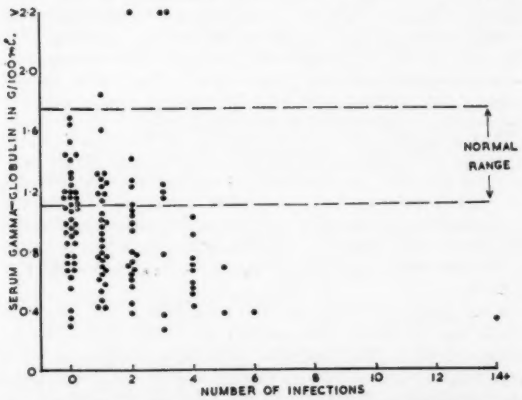

FIG. 4.—Relationship between serum gamma-globulin level determined by electrophoresis, and number of infections occurring during preceding year in 110 patients with chronic lymphatic leukaemia.

the level was reduced, and this takes no account of two patients, both with low gamma-globulin concentrations, in whom the first infection was fatal.

Measurement of the gamma-globulin concentration by paper electrophoresis is inaccurate with low levels (Gell, 1957), and it was in these patients that immunological methods proved valuable. We have followed the standards laid down for the M.R.C. Hypogammaglobulinaemia Therapeutic Trial in regarding values of under 0.2 g./100 ml. obtained by immunological methods as dangerously low (Squire, 1960).

Three patients with levels as low as this have been treated with gamma-globulin as used in the M.R.C. trial: it was prepared by the method of Kekwick and Mackay (1954) and supplied by the Blood Products Laboratory of the Lister Institute. The gamma-globulin was given by intramuscular injection, starting with a loading dose of 0.15 g./kg. body weight given over the first week, followed by a maintenance dose of 0.025 g./kg. weekly.

Case 1.—A woman, now aged 65, was found to have chronic lymphatic leukaemia in 1955. In 1956 she began to suffer from infections in the form of boils, paronychia, otitis media, bronchitis, and pneumonia, which increased in severity and frequency until treatment with gamma-globulin was started in April, 1959. The number of infective episodes before treatment was: April, 1956, to March, 1957, 6; April, 1957, to March, 1958, 11; April, 1958, to March, 1959, 18. During treatment the number was: April, 1959, to March 1960, 4; April, 1960, to March, 1961, 3. During the first three months of treatment two severe infections occurred, possibly because she received only a maintenance dose from the outset owing to difficulties in giving her a loading dose as an out-patient. In the last 21 months she has had only five mild episodes of infection. Treatment has thus reduced the incidence of infections from 18 to between 3 and 4 a year. She has received 1.5 g. of gamma-globulin in a volume of 15 ml. weekly by two intramuscular injections of 7.5 ml. each. The injections are unquestionably painful, but she is convinced that she feels better and that the treatment is worth while. She has gained weight, and even when an infection occurs it is neither so long nor so severe as those she had previously. Before treatment the serum gamma-globulin concentration was 0.16 g./100 ml. by the agar diffusion method and 0.19 g. by the neutralization test. It is being maintained at 0.28–0.5 g./100 ml.

Case 2.—A woman, aged 70 at the time of her death in 1959, underwent splenectomy for hypersplenism in 1950. The excised organ showed changes regarded as lymphosarcomatous. Later, lymphocytic infiltration of the bone-marrow and peripheral lymphocytosis established the diagnosis of chronic lymphatic leukaemia. During 1958 she suffered from six bacterial infections: three boils, one attack of pneumonia, and two abscesses. One gluteal abscess lasted three months. In 1959 her serum gamma-globulin concentration was found to be 0.14 g./100 ml. by the agar diffusion method and 0.10 g./100 ml. by the neutralization test, and gamma-globulin treatment was started. After three months the level had risen to 0.32 g./100 ml., but although she felt better she declined further treatment because the injections were so painful. Her condition deteriorated; she lost weight and died three months later after a succession of infections, including conjunctivitis, boils, pneumonia, and cystitis.

Case 3.—A woman, aged 67 at the time of her death in 1960, was found to have chronic lymphatic leukaemia in 1943. With the exception of pneumonia in 1947 she had suffered from no bacterial infections until her last admission to hospital in 1960. At this time an infection of the upper respiratory tract was followed by pneumonia and she was then found to have a serum gamma-globulin level of 0.08 g./100 ml. by the agar diffusion method and 0.07 g. by the neutralization test. In spite of full doses of gamma-globulin and the appropriate antibiotics she died a week later. Two days after the start of treatment the serum gamma-globulin concentration had risen to 0.32 g./100 ml.

Factors Responsible for Hypogammaglobulinaemia

In a search for possible causes of the hypogammaglobulinaemia in these patients an attempt was made to assess the importance of the duration, severity, and extent of the disease, the treatment received, and the age and sex of the patient. The first three are difficult to measure and arbitrary criteria have been used. The duration of the disease has been taken as the interval between diagnosis and testing and the severity as indicated by the interval between testing and death. The extent of the disease is expressed by the number of anatomical sites involved at the time of testing. The patients were placed in 10 grades, grade 10 indicating that disease was present in 10 or more sites.

The level of circulating gamma-globulin determined by paper electrophoresis was clearly related to the duration of the disease (Fig. 5). The correlation coefficient $r = -0.239$ ($P<0.05$). All patients known to have had chronic lymphatic leukaemia for five years or more had hypogammaglobulinaemia.

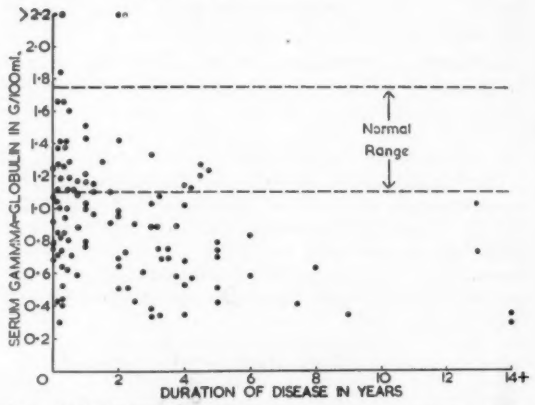

Fig. 5.—Relationship between serum gamma-globulin level, determined by electrophoresis, and duration of disease in 110 patients with chronic lymphatic leukaemia ($r = -0.239$; d.f. = 108; $P<0.05$).

There appeared to be no correlation between the level of gamma-globulin in the serum and the subsequent duration of life. Two patients with normal levels died within a week of testing, while two survived a year with reduced levels. However, only 10 of the 110 patients have died; thus the importance of this factor cannot be accurately assessed.

No correlation could be found between the extent of disease and the serum gamma-globulin concentration (Fig. 6). The correlation co-efficient $r = +0.058$. Of the 21 patients in grades 8–10, 13 (62%) had hypogammaglobulinaemia, compared with 28 (64%) of 44 in grades 1 and 2.

The Table shows that treatment was not responsible for the abnormal gamma-globulin levels. There was no significant difference between the treated and untreated nor between those who received different forms of treatment.

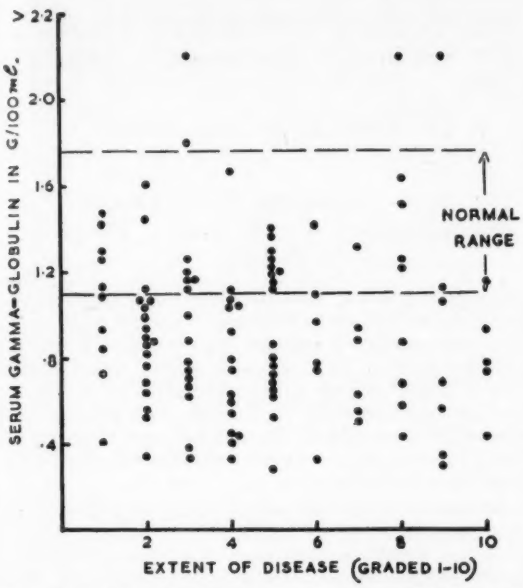

FIG. 6.—Relationship between serum gamma-globulin level, determined by electrophoresis, and extent of disease in 110 patients with chronic lymphatic leukaemia ($r = +0.058$, which is not significant).

Serum Gamma-globulin Levels in Relation to Treatment in Chronic Lymphatic Leukaemia

	Total Patients	Reduced Level	Normal Level	Raised Level
Treated group:				
Steroids only	3	2	1	0
Radiotherapy only ..	11	8	3	0
Cytotoxic drugs only ..	14	8	5	1
More than one form of treatment	26	20	5	1
Total	54	38 (70%)	14 (26%)	2 (4%)
Untreated group	56	36 (64%)	18 (32%)	2 (4%)
Both groups	110	74 (67%)	32 (29%)	4 (4%)

No correlation was found between the age of the patient and the gamma-globulin concentration ($r = -0.15$), nor was there any difference between the sexes.

In these patients, therefore, the gamma-globulin concentration of the serum may have been related to the duration of the disease, falling with the advance of time; but no association could be established with any of the other variables considered.

Discussion

From this and other published series it is seen that hypogammaglobulinaemia is a common occurrence in chronic lymphatic leukaemia. It is not due to such extraneous causes as age, sex, or treatment, and must therefore be regarded as an essential product of the disease. There is no doubt that in these patients the gamma-globulin concentration of the serum tends to fall with the progress of time: not only is there a statistically significant correlation between the duration of the disease and the gamma-globulin level, but in individual patients tested at regular intervals the values have become progressively lower. This association with the duration of the disease has been noted by others (Ultmann *et al.*, 1959; Hudson and Wilson, 1960).

The deficiency can be made good by intramuscular injection of gamma-globulin, and the results of such treatment in three patients are reported in this paper. The first patient proved that the treatment was effective enough to make the discomfort of the injections worth tolerating, the second established the danger of stopping treatment, and in the third disaster might have been averted if treatment had been started earlier.

The results indicate that in all patients who have had chronic lymphatic leukaemia for more than four years the serum gamma-globulin concentration should be measured at least every six months. If the level is dangerously low intramuscular injections of gamma-globulin should be started at the first indication of infection. Benefit from such injections has been recorded by others (Shaw *et al.*, 1960). However, the report of a hypersensitivity reaction (Diamond and Miller, 1961) enjoins caution, although such an event has not been noted with gamma-globulin prepared in this country (Squire, 1960).

Patients with acute leukaemia are also liable to infection, but probably from a different cause. In this disease the gamma-globulin levels may be raised (Corsini and Manfredi, 1957; La Grutta, 1957; Fahey and Boggs, 1960), but hypogammaglobulinaemia is rare and never more than slight (Teitelbaum *et al.*, 1959; Fahey and Boggs, 1960). Antibody formation, too, is only slightly impaired, normal, or even increased (Weinstein and Fitz-Hugh, 1935; Larson and Tomlinson, 1953; Silver *et al.*, 1960). There is no correlation between the frequency of bacterial infections and the serum gamma-globulin level (Fahey and Boggs, 1960) or the degree of antibody response (Silver *et al.*, 1960). Presumably in acute leukaemia infection results from a failure in the cellular defences of the body rather than of the humoral immunity mechanisms, and treatment with gamma-globulin would be of little benefit.

Summary

The serum gamma-globulin concentration has been determined by paper electrophoresis in 110 patients with chronic lymphatic leukaemia. In 29% the level was normal, in 67% reduced, in 3% raised with no excess of macroglobulin, and 1% had macroglobulinaemia.

The level of serum gamma-globulin was related to the duration of the disease, tending to fall with the passage of time, and all those known to have had chronic lymphatic leukaemia for five years or more had low levels.

In one patient treatment with intramuscular injection of gamma-globulin has reduced both the number and the severity of bacterial infections. This treatment has the disadvantage that the injections are painful and need to be given once a week.

It is suggested that the serum gamma-globulin level should be measured at frequent intervals and that patients in whom it is below 0.2 g./100 ml. by immunological methods should be treated promptly with gamma-globulin if bacterial infection develops.

Our thanks are due to Professor J. R. Squire and Dr. W. d'A. Maycock for supplies of gamma-globulin and much useful advice; to Dr. P. L. Mollison, Dr. J. F. Soothill, Dr. A. B. Anderson, Dr. I. McIntyre, Mr. M. P. Curwen, Dr.

A. E. Mourant, and Professor N. H. Martin for their help; and to many colleagues for permission to study their patients.

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"In recent years I have noted with interest the almost complete disappearance of the word *before*. In medical circles it is supplanted by the more cumbersome pseudo-elegant 'prior to.' In case presentations I have frequently heard the expression 'prior to' used from 20 to 50 times before the good old Anglo-Saxon word *before* was used. I have no idea what to make of this important observation." William B. Bean, in *Arch. intern. Med.*, 1961, **108**, 4.

CIRCULATING ANTIBODIES TO MILK PROTEINS IN ULCERATIVE COLITIS

BY

K. B. TAYLOR,* D.M., M.R.C.P.

AND

S. C. TRUELOVE, M.D., F.R.C.P.

Nuffield Department of Clinical Medicine, The Radcliffe Infirmary, Oxford.

During the last few years some patients with ulcerative colitis have been found to improve greatly when cow's milk has been totally excluded from the diet. In several of these patients, milk was reintroduced into the diet, and in every instance this was followed in the course of a few days or weeks by a frank attack of ulcerative colitis (Truelove 1961). These observations prompted us to look for the presence of antibodies to cow's milk proteins in that disease.

Materials Tested.—The chief proteins of milk—casein, α-lactalbumin, and β-lactoglobulin—were made available to us in a highly purified form by Dr. R. Aschaffenburg, of the National Institute for Research in Dairying, who has described the methods of preparation (Gunther *et al.*, 1960).

Tests Performed.—Sera were collected from patients with ulcerative colitis in all stages of the disease, from severe symptoms to prolonged freedom from symptoms. The sera of healthy subjects were collected from laboratory staff and from the healthy relatives of general medical in-patients. These sera were tested for the presence of antibodies by the coated-tanned-red-cell technique of Boyden (1951) as modified by Witebsky and Rose (1956), by the gel-diffusion method of Ouchterlony (1948), and, in some cases, by the passive cutaneous anaphylaxis reaction in guinea-pigs (Ovary, 1958).

Results

Ouchterlony Gel-diffusion Test.—The sera from 75 patients with ulcerative colitis and from 50 healthy subjects were tested against solutions of casein, lactalbumin, and lactoglobulin. The tests were repeated under a variety of conditions, varying the strengths of the milk proteins and of the sera. All the results were negative. In other words, this test failed to show any evidence of precipitating antibodies to individual milk proteins in either ulcerative colitis or in health.

Passive Cutaneous Anaphylaxis Test.—This test was performed on guinea-pigs by intravenous injection of 1% lactoglobulin, together with 1% Evans blue, four hours after intradermal injection of a number of sera which had shown either negative or strongly positive reactions to lactoglobulin by the coated-tanned-red-cell technique. The results were negative in all cases. It is known, however, that human sera do not always give strong reactions with this test (Ovary, 1958).

Tanned-red-cell Test.—The sera of 75 patients with ulcerative colitis and of 50 healthy subjects were tested against each of the three milk proteins. For each subject the serum was tested in serial dilution at concentrations of 1/20, 1/200, 1/2,000, and 1/20,000. It was found by experiment that optimal results were obtained by using each of the three milk proteins in a concentration

*Member of the M.R.C. Gastroenterology Research Unit.

of 0.5% in 0.1 M phosphate-saline buffer at *p*H 6.4. Repeated tests showed that the results were reproducible with only slight variation in the scoring of titres. The results of each reaction were scored as strongly positive (++), positive (+), doubtful positive (±), and negative (−). The reaction was read after two and after 24 hours. In presenting the results the highest dilution of serum showing a positive reaction at either two or 24 hours has been taken as the titre of antibodies present. Doubtful reactions have been counted as negative. However, it is worth mentioning that all the conclusions remain unaltered if doubtful reactions are counted as positive ones and if the results of reading the tests after two and after 24 hours are taken separately.

Difference Between Ulcerative Colitis Patients and Normal Subjects

Among the normal subjects and among the patients with ulcerative colitis a wide variation of reactions to the milk proteins was found. In both groups there were subjects with negative reactions to all three proteins, some with reactions to one protein, some with reactions to two, and some with reactions to all three. However, when the two groups were compared, striking differences were found to exist. Table I and Fig. 1 show that positive reactions with high dilutions of serum occurred much more often in patients with ulcerative colitis than in normal subjects. With casein, seven times as many ulcerative colitis patients showed positive reactions in sera diluted 1/20,000. With lactalbumin, the difference, although definite, was less striking and did not quite reach conventional levels of statistical significance.

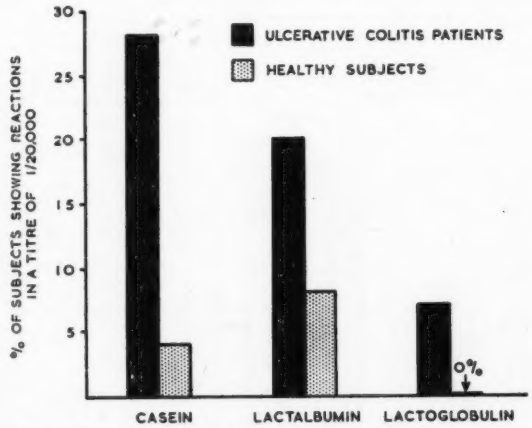

FIG. 1.—Showing the increased frequency of high-titre reactions to milk proteins in ulcerative colitis.

With lactoglobulin, the difference was striking, with seven times the incidence of reactions in high dilution of serum (1/2,000 or 1/20,000) in ulcerative colitis as in health.

Independence of the Reactions to Separate Milk Proteins

An obvious point worth examination is whether the reactions to individual milk proteins are highly specific or whether a positive reaction to one milk protein implies a high probability of positive reactions to the others.

Table II shows the association between these reactions in normal subjects and ulcerative colitis patients. For simplicity and ease of presentation the levels of reaction are reduced to three—namely, negative, positive in low titre (1/20 or 1/200), and positive in high titre (1/2,000 or 1/20,000). It can be seen that there is a certain measure of association but that it is not pronounced. In other words, these reactions are specific to the individual proteins, and a high level of reaction to one of them may coexist with negative reactions to the others. This conclusion applies equally to the patients with ulcerative colitis and to healthy subjects. We have recorded these data in full because we know of no other comparable study.

TABLE II.—*Association Between Reactions to Different Antigens in Ulcerative Colitis and in Health*

		Normals				Ulcerative Colitis			
1. *Casein and Albumin*									
		Albumin				Albumin			
		Neg.	Low	High	Totals	Neg.	Low	High	Totals
Casein	Neg. ..	14	4	2	20	7	3	3	13
	Low ..	9	9	6	24	10	8	8	26
	High ..	1	2	3	6	5	14	17	36
		24	15	11	50	22	25	28	75
2. *Casein and Globulin*									
		Globulin				Globulin			
		Neg.	Low	High	Totals	Neg.	Low	High	Totals
Casein	Neg. ..	16	4	—	20	9	3	1	13
	Low ..	19	5	—	24	13	10	3	26
	High ..	2	3	1	6	14	15	7	36
		37	12	1	50	36	28	11	75
3. *Albumin and Globulin*									
		Globulin				Globulin			
		Neg.	Low	High	Totals	Neg.	Low	High	Totals
Albumin	Neg. ..	22	2	—	24	18	3	1	22
	Low ..	8	7	—	15	10	12	3	25
	High ..	7	3	1	11	8	13	7	28
		37	12	1	50	36	28	11	75

TABLE I.—*Reactions of Normal and Ulcerative Colitis Sera to Purified Milk Proteins with Coated Tanned-red-cell Test*

	Casein		Lactalbumin		Lactoglobulin	
	Normal Subjects	Ulcerative Colitis	Normal Subjects	Ulcerative Colitis	Normal Subjects	Ulcerative Colitis
Negative ..	20 (40%)	13 (17·3%)	24 (48%)	22 (29·3%)	37 (74%)	36 (48·0%)
1/20	10 (20%)	10 (13·3%)	7 (14%)	12 (16·0%)	8 (16%)	13 (17·3%)
1/200	14 (28%)	16 (21·3%)	8 (16%)	13 (17·3%)	4 (8%)	15 (20·0%)
1/2,000 ..	4 (8%)	15 (20·0%)	9 (18%)	13 (17·3%)	1 (2%)	6 (8·0%)
1/20,000 ..	2 (4%)	21 (28·0%)	2 (4%)	15 (20·0%)	0 (0%)	5 (6·7%)
Total ..	50 (100%)	75 (100%)	50 (100%)	75 (100%)	50 (100%)	75 (100%)
Statistical significance of the differences	$\chi^2 = 19·46$ Degrees of freedom = 4 P < 0·001 Highly significant		$\chi^2 = 8·605$ Degrees of freedom = 4 0·1 > P > 0·05 Not significant		$\chi^2 = 11·361$* Degrees of freedom = 3 P < 0·01 Highly significant	

* Combining the last two rows in view of the small numbers.

Analysis of the Differences Between Ulcerative Colitis and Health

In view of the marked liability of the ulcerative colitis patients to show a higher incidence of strongly positive reactions than normal subjects, the data have been extensively analysed in a search for explanations of the difference. The following points have emerged.

Effect of Age and Sex

The differences between the ulcerative colitis and the healthy subjects are not related to the age-and-sex composition of the two groups, as can be seen from two facts. First, in age-and-sex composition the two groups were closely similar, as shown in Tables III and IV. Secondly, when the results of the test are considered for separate age-groups and for each sex in turn, it does not appear that age and sex have any close relationship to the liability to positive reactions—at any rate, in the age-groups now studied—either in ulcerative colitis or in health. In the interests of brevity these results are not reported in full, but Table V, which shows the reactions to casein in patients with ulcerative colitis by separate age-groups, is presented as an example.

TABLE III.—*Age Composition of the Groups*

Age-group (Years)	Normal Subjects	Patients with Ulcerative Colitis
<30	10 (20%)	15 (20·0%)
30–39	11 (22%)	23 (30·7%)
40–49	14 (28%)	15 (20·0%)
50–	15 (30%)	22 (29·3%)
Total ..	50 (100%)	75 (100%)

TABLE IV.—*Sex Composition of the Groups*

	Normal Subjects	Patients with Ulcerative Colitis
Male	20 (40%)	32 (42·7%)
Female	30 (60%)	43 (57·3%)
	50 (100%)	75 (100%)

TABLE V.—*Reactions to Casein in Patients with Ulcerative Colitis by Separate Age-groups, Showing the Negligible Effects of Age on the Reaction*

Age-group (Years)	Negative	1/20	1/200	1/2,000	1/20,000	Total	% with High-titre Reactions
<30 ..	1	3	6	3	2	15	33·3
30–39 ..	4	0	4	7	8	23	65·2
40–49 ..	5	3	1	2	4	15	40·0
50– ..	3	4	5	3	7	22	45·5
Total	13	10	16	15	21	75	

Features of Ulcerative Colitis

The second main question was whether it was possible to define a subgroup of the ulcerative colitis patients with a sufficiently high incidence of positive reactions to account for the difference between these subjects as a whole and the normal subjects. A considerable amount of clinical information was available for all the ulcerative colitis patients, and a variety of possible factors was considered. All our attempts to find a reasonable explanation for the difference have failed, but some of the points which emerge are worth mentioning.

1. *Effect of Diet.*—Twenty-two of the patients were on a milk-free diet and had been so for periods varying from a minimum of three months up to a maximum of three years. There was no appreciable difference between these patients and the remainder. Table VI, which shows only the reactions to casein, is an example. Taking only reactions at high titre to casein (1/2,000 or 1/20,000), it can be seen that there were 45% among those on a milk-free diet compared with 49% among those on a normal diet. Fig. 2 illustrates the similarity of results for all three proteins.

TABLE VI.—*Showing the Similar Distribution of Reactions to the Individual Milk Proteins Among Patients with Ulcerative Colitis, on a Milk-free Diet and on a Normal Diet*

Specific Protein	Diet	Level of Reactions: Negative	1/20	1/200	1/2,000	1/20,000	Total No. of Patients	% with High-titre Reactions
Casein	Milk-free	3	3	6	6	4	22	45·5
	Normal	10	7	10	9	17	53	49·0
Lact-albumin	Milk-free	8	3	4	4	3	22	31·8
	Normal	14	9	9	9	12	53	39·6
Lacto-globulin	Milk-free	9	4	6	1	2	22	13·6
	Normal	27	9	9	5	3	53	15·1

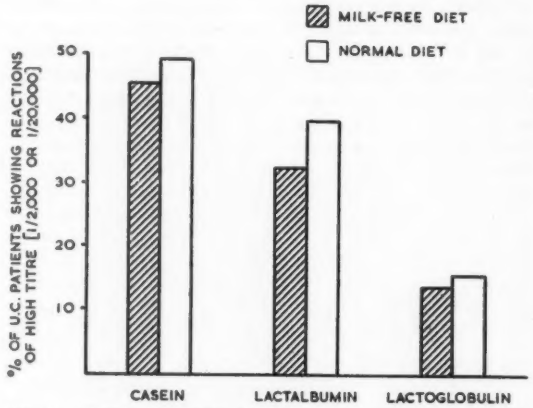

FIG. 2.—Showing the close similarity between the patients with ulcerative colitis on a normal diet and those on a milk-free diet with respect to the proportion showing high-titre reactions to the specific milk proteins.

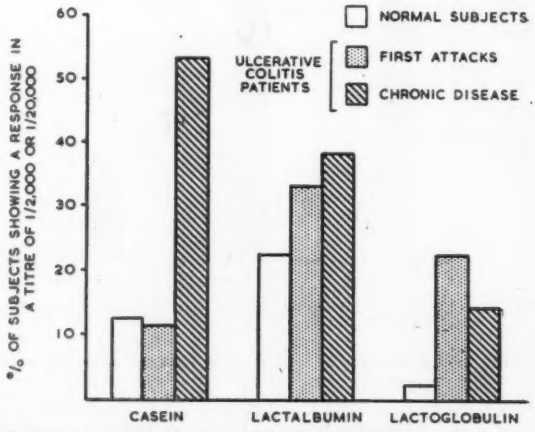

FIG. 3.—Showing that the response to casein differs markedly between patients with a first attack of ulcerative colitis and those with a relapse of established disease, whereas there is little difference with lactalbumin and lactoglobulin.

2. *Radiological Extent of the Disease.*—The maximum extent of the disease at any time in its history was available on radiological evidence. Twenty-eight of the patients had disease which had apparently never extended beyond the distal colon, 14 had more extensive disease without the whole colon being involved, and 33 had evidence of involve-

ment of the entire colon. There was no obvious difference in the reactions to milk proteins between these three subgroups.

3. *Effect of Steroid Treatment.*—At the time when the sera were collected 41 patients were receiving no steroids, 13 were on local corticosteroid treatment, 7 on systemic corticosteroid, and 14 on combined systemic and local treatment. There was no obvious effect upon the distribution of reactions to milk proteins. Table VII shows the results in simplified form by comparing patients on any type of corticosteroid treatment with those on no treatment.

TABLE VII.—*Showing Lack of Effect of Steroid Therapy*

Specific Protein	Treatment	Level of Reactions: Negative	1/20	1/200	1/2,000	1/20,000	Total No. of Patients	% with High-titre Reactions
Casein	Steroid	6	6	5	5	12	34	50·0
	None	7	4	11	10	9	41	46·3
Lactalbumin	Steroid	5	7	8	8	6	34	41·2
	None	17	5	5	5	9	41	34·1
Lactoglobulin	Steroid	11	4	12	3	4	34	20·6
	None	25	9	3	3	1	41	9·8

4. *Activity of the Disease.*—There was no appreciable difference beween the distribution of reactions in patients with active disease and those who were in clinical remission (Table VIII).

TABLE VIII.—*Showing Lack of Effect of Clinical Activity of the Disease*

Specific Protein	Clinical State of Disease	Level of Reactions: Negative	1/20	1/200	1/2,000	1/20,000	Total No. of Patients
Casein	Active	4	5	8	3	7	27
	Quiescent	9	5	8	12	14	48
Lactalbumin	Active	9	4	7	3	4	27
	Quiescent	13	8	6	10	11	48
Lactoglobulin	Active	16	3	5	2	1	27
	Quiescent	20	10	10	4	4	48

5. *Chronicity of the Disease.*—The one factor which was found to influence the levels of antibody was the chronicity of the disease, and this applied only to casein. Among the nine patients from whom sera were taken during or shortly after the first attack of the disease, the titres of antibody to casein resembled the values found in normal subjects, whereas the patients with established chronic ulcerative colitis showed a marked preponderance of high-titre reactions. This difference between first-attack cases and chronic cases was significant statistically, but the number of first-attack cases is small and this relationship deserves more extensive study. No similar relationship existed for lactalbumin and lactoglobulin (Table IX).

6. *Interrelationships Between Various Factors.*—The various factors just dealt with individually have been considered simultaneously during the analysis and we are satisfied that the negative conclusions are not the result of interactions. As an example, if activity of the disease and steroid treatment are taken account of simultaneously in relation to reactions to casein, we arrive at the following:

Activity of Disease	Steroid Treatment	No. of Patients	No. with High Titre	%
Active	−	19	6	31·6
,,	+	8	4	50·0
Quiescent	−	22	13	59·1
,,	+	26	13	50·0

Difference Between Ulcerative Colitis Patients and Normal Subjects When the Milk Proteins are Considered Collectively

We have so far considered the reactions to the individual milk proteins separately. We have repeated the analysis, taking the highest titre registered by each subject for any of the three proteins. This has shown a striking difference between ulcerative colitis and health (Table X). More than five times as many patients with ulcerative colitis showed a reaction at a titre of 1/20,000 as did normal subjects. However, the complete analysis showed that the type of diet, activity of disease, radiological extent of disease, and steroid treatment did not explain the difference.

TABLE X.—*Difference Between Ulcerative Colitis Patients and Healthy Subjects When the Highest Titre of Reaction Against any of the Three Milk Proteins is Taken*

Highest Titre	Normal: No.	Normal: %	Ulcerative Colitis: No.	Ulcerative Colitis: %
Negative	14	28·0	6	8·0
1/20	7	14·0	5	6·7
1/200	15	30·0	16	21·3
1/2,000	10	20·0	16	21·3
1/20,000	4	8·0	32	42·7
Total	50	100·0	75	100·0

$\chi^2 = 22·6$. Degrees of freedom, 4. $P < 0·001$.

Discussion

This study has shown an unequivocal difference between patients with ulcerative colitis and healthy subjects with respect to the level of circulating antibodies to milk proteins. The difference is not an absolute one,

TABLE IX.—*Showing Serum Reactions in First Attacks and Chronic Established Disease*

	Length of History (Years)	Level of Reactions: Negative	1/20	1/200	1/2,000	1/20,000	Total No. of Patients	% with High-titre Reactions
Casein								
First attack	<1	3	1	4	—	1	9	11·1
Chronic disease	1–3	3	4	4	2	6	19	42·1
	4–10	4	4	4	10	8	30	60·0 } 53·0
	>10	3	1	4	3	6	17	52·9
		13	10	16	15	21	75	
Albumin								
First attack	<1	5	—	1	3	—	9	33·3
Chronic disease	1–3	8	5	3	2	1	19	15·8
	4–10	3	4	6	5	12	30	56·7 } 37·9
	>10	6	3	3	3	2	17	29·4
		22	12	13	13	15	75	
Globulin								
First attack	<1	6	—	1	—	2	9	22·2
Chronic disease	1–3	14	2	2	—	1	19	5·3
	4–10	9	9	6	4	2	30	20·0 } 13·6
	>10	7	2	6	2	—	17	11·8
		36	13	15	6	5	75	

because some normal subjects show these circulating antibodies in high dilution of serum. Nevertheless, in statistical terms the difference is impressive.

In looking for an explanation for the difference, we have considered a number of possibilities. First, ulcerative colitis might be the expression of a food allergy in a certain proportion of patients, a view first put forward by Andresen in 1926. Subsequently he claimed that milk was the foodstuff most commonly responsible for the disease (Andresen, 1942). The present study does not yield much support for this viewpoint. Healthy subjects can have circulating antibodies in high titre against milk proteins even though they have them less commonly than patients with ulcerative colitis. It has been known for many years that immunological reactions to milk proteins may be exhibited by infants fed on cow's milk (Schloss, 1924–5; Du Bois, Schloss, and Anderson, 1925). These reactions are presumably due to the absorption of proteins which have not been sufficiently digested to lose antigenicity. Ulcerative colitis is uncommon in childhood, but it is interesting that a small cluster of cases occur in early infancy (Platt *et al.*, 1960), which conceivably could be due to failure to develop tolerance to certain food proteins.

Secondly, it is possible that immunological reactions to food proteins might perpetuate ulcerative colitis once it has developed, even though food proteins may not be a direct causative factor. So far as milk proteins are concerned, the fact that patients in whom the disease was quiescent resembled serologically those with active disease is against this possibility if one assumes that the circulating antibodies are any index of total immunological response.

Thirdly, we considered the possibility of the increased frequency of high-titre reactions in ulcerative colitis being a consequence of the disease. The one finding of the present study which supports this possibility is the fact that patients with a first attack of ulcerative colitis showed normal levels of circulating antibodies to casein, whereas patients with chronic disease showed a much greater frequency of high-titre reactions than normal subjects. Increased absorption of antigenic protein might occur in this disease for at least two separate reasons—namely, depressed proteolytic activity in the upper gastro-intestinal tract, or more facile absorption of undigested protein by the inflamed colonic mucosa. We have some evidence on both of these points. So far as proteolysis in the upper gastro-intestinal tract is concerned, we have studied the serological reactions to milk proteins of patients with pernicious anaemia, a disease in which gastric proteolysis is much reduced. Table XI shows that they resemble normal subjects rather than patients with ulcerative colitis. This finding only disposes of depressed gastric proteolysis as a factor and takes no account of the possibility that small-intestinal proteolysis may be depressed in ulcerative colitis. We have no evidence on this point, but, even assuming that both gastric and intestinal proteolysis is normal, about 10% of the dietary protein reaches the bottom of the small intestine without being digested (Borgström *et al.*, 1957) and increased absorption might occur through the inflamed colonic mucosa. If this were so, one might expect that the sera of patients with ulcerative colitis would show the same abnormally high frequency of high-titre reactions to other dietary proteins. However, when egg-white protein was tested in the same way as the milk proteins, the differences between the findings in normal subjects and ulcerative colitis patients were trivial (Table XII).

TABLE XII.—*Showing Similar Distribution of Serum Reactions to Egg-white in Normal Subjects and Patients with Ulcerative Colitis*

	Level of Reaction			Total
	Negative	Low	High	
Normal subjects	28	16	6	50
Ulcerative colitis	24	16	10	50
Total	52	32	16	100

$\chi^2 = 1{\cdot}31$. Degrees of freedom, 2. $P > 0{\cdot}05$.

Finally, we considered the possibility that the serological reactions to milk were an epiphenomenon indicative of a more general disturbance of immunological responses in ulcerative colitis, although not, in themselves, being a direct cause or consequence of the disease. Our failure to distinguish any significant relationship between the serological reactions and various clinical features of the disease are compatible with this view. On the other hand, our findings with egg-white protein are against it, although the various food-proteins may differ sharply both in their patterns of digestion and in their antigenicity.

This final possibility is supported by the most recent findings in relation to autoantibodies in ulcerative colitis. Broberger and Perlmann (1959) and Perlmann and Broberger (1960) demonstrated the presence of circulating and lymph-node antibodies to extracts of human foetal colon in ulcerative colitis, while Thayer *et al.* (1960) have demonstrated the existence of antinuclear globulins in this disease. However, Asherson and Broberger (1961) have now shown that antibodies to human colon are not confined to ulcerative colitis but also occur in patients with diffuse lupus erythematosis and rheumatoid arthritis, in which diseases antinuclear globulins were first described.

The only type of immune response detected in this study has been the presence of circulating antibodies. The gel-diffusion test for precipitating antibodies has been uniformly negative. The relationship between circulating antibodies and abnormal tissue reactions

TABLE XI.—*Showing that the Titres of Circulating Antibodies to Milk Proteins in Pernicious Anaemia Patients Resemble those in Normal Subjects Rather than those Found in Ulcerative Colitis Patients. Percentage Distribution of Subjects Showing Negative Reactions, Low-titre Reactions* (1/20 *or* 1/200), *and High-titre Reactions* (1/2,000 *or* 1/20,000)

	Casein			Albumin			Globulin		
	Normal Subjects	Pernicious Anaemia	Ulcerative Colitis	Normal Subjects	Pernicious Anaemia	Ulcerative Colitis	Normal Subjects	Pernicious Anaemia	Ulcerative Colitis
Negative	40	41·4	17·3	48	60	29·3	74	90·0	48·0
Low	48	34·5	34·6	30	20	33·3	24	6·7	37·3
High	12	24·1	48·0	22	20	37·3	2	3·3	14·7
Total ..	100	100	100	100	100	100	100	100	100

remains obscure. Parish *et al.* (1960) have presented evidence of the presence in infancy of circulating antibodies to milk proteins and have attempted to relate them to the occurrence of sudden "cot death," resulting from aspiration of even small quantities of regurgitated cow's milk. They supported their view by animal experiments in which guinea-pigs sensitized to milk proteins by single intraperitoneal injection of milk died suddenly when small quantities of milk were introduced into the trachea. They postulated that circulating or other antibodies to milk might sensitize the tissues of babies.

We have sensitized guinea-pigs to each of the three milk proteins used in the experiments in this paper, employing the complete Freund adjuvant technique and multiple intradermal and subcutaneous injections. The dose of protein in each instance was 10 mg. Our findings are shown in Table XIII. Skin tests were positive at 42 days. Precipitating antibodies were found only in the case of lactalbumin. The coated-tanned-red-cell test was positive in high titre against the corresponding antigens in the case of casein and lactalbumin, but was positive only in low titre in the case of lactoglobulin.

TABLE XIII.—*Findings in Guinea-pigs Sensitized to Individual Cow's Milk Proteins*

Antigen	Skin Test (Performed 42 Days after Sensitizing Injection)	Precipitins by Gel-diffusion Test	Coated Tanned Red Cell Test Against Appropriate Antigen
Casein	+	−	1/20,000
α-Lactalbumin ..	Not done	+	1/20,000
β-Lactoglobulin ..	+++	−	1/200

The animal results differ sharply from the reactions in man. Skin tests to the common foodstuffs have been made by our colleague, Dr. R. M. Morris-Owen, in patients with ulcerative colitis and a control group of subjects, using proprietary test extracts. Occasional positive reactions were present in both groups of subjects, but there was no suggestion of an unduly high frequency of positive skin reactions in ulcerative colitis. Similar tests with the purified milk proteins have not yet been made.

Summary

A study has been made of some immunological reactions to purified cow's-milk proteins in ulcerative colitis and in health.

The Ouchterlony gel-diffusion test was uniformly negative.

The passive cutaneous anaphylaxis test in guinea-pigs was also negative.

The coated-tanned-red-cell test showed the presence of circulating antibodies in some normal subjects and in some patients with ulcerative colitis. The proportion of subjects showing antibodies in high dilution of sera was much greater in ulcerative colitis than in health.

Analysis of the data in relation to various clinical features of the 75 patients with ulcerative colitis showed that the increased incidence of high-titre reactions to milk proteins could not be explained on the basis of (*a*) age and sex of the subjects studied; (*b*) effect of a milk-free diet; (*c*) activity or quiescence of the disease; (*d*) radiological extent of the disease; (*e*) corticosteroid therapy. The one feature which has emerged is that, for casein only, patients in their first attack of ulcerative colitis resemble normal subjects and a marked preponderance of high-titre reactions occurs only among patients with established chronic disease.

These findings are discussed in relation to immunological concepts of disease.

We are very grateful to Dr. R. Aschaffenburg for making a gift of the purified milk proteins used in this study. We thank Miss Marjory Alcock for technical assistance. We also thank our colleague, Dr. John Morton, and Dr. J. G. Feinberg, of Beecham Research Laboratories, who gave us technical advice on certain aspects of the study. Some of the expenses were covered by a grant from the Medical Research Council.

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EARLY WEANING IN THE AETIOLOGY OF ULCERATIVE COLITIS

A STUDY OF FEEDING IN INFANCY IN CASES AND CONTROLS

BY

E. D. ACHESON, D.M., M.R.C.P.

AND

S. C. TRUELOVE, M.D., F.R.C.P.

Nuffield Department of Clinical Medicine, University of Oxford

(From the Radcliffe Infirmary, Oxford)

During the past few years it has been found that some of the patients with ulcerative colitis attending the Nuffield Department of Clinical Medicine have shown a very beneficial clinical response when cow's milk and cheese have been entirely excluded from the diet. In five of these patients, milk or cheese has been reintroduced into the diet—in one patient on two separate occasions—and in every instance this was followed by a sharp clinical relapse of the ulcerative colitis. There was a strong positive correlation between the time the patient had been symptom-free on a milk-free diet and the time taken to relapse when milk was reintroduced (Truelove, 1961).

These clinical observations prompted us to consider a number of possible explanations. One of them was the possibility that liability to ulcerative colitis might have some connexion with artificial feeding in infancy. The present article is concerned with some observations we have made on this topic.

Material and Method

The material of the study consisted of all the patients with definite ulcerative colitis who attended the Nuffield Department of Medicine, either as in-patients or as out-patients, in the first six months of 1961. Patients in whom the disease had remained localized to the rectum or in whom the diagnosis was in doubt were not included. We were left with 152 patients with classical disease. Each of these was interviewed personally by one of us (E.D.A.) and was asked a number of standard questions, the answers to which were the basis of this paper. The questions were:

1. Were you breast-fed or bottle-fed from birth?
2. If breast-fed, how old were you when breast-feeding was stopped?
3. Is your mother or any other person with first-hand evidence about your infant-feeding alive and prepared to answer a postal questionary?
4. What is your (or your husband's or father's) exact current occupation?
5. How many live-born brothers and sisters did you have and what is your rank of birth in the family?

Where first-hand evidence was available the parent or other relative was sent an additional questionary by post, which asked for detailed information about the patient's feeding as an infant, including the date at which breast-feeding was stopped and the date at which artificial feeding was begun if this was different. With the questionary was sent a standard covering letter stating that the propositus was a patient of the department and that a research survey was being carried out to determine the infant-feeding history in our patients.

Control patients who were not suffering from ulcerative colitis were selected from general medical out-patients and in-patients of the Nuffield Department of Medicine. They were given an identical interview by the same person, and an identical postal questionary was sent to their relatives. They were matched for age and sex, and the two series of interviews ran concurrently.

It is convenient at this point to give definitions of the terms and conventions we used.

(*a*) A patient was regarded as having ceased to be breast-fed as soon as artificial feeding was started. Thus a period during which breast-feeding was supplemented by artificial feeds did not count as breast-feeding.

(*b*) Breast-feeding was considered to have been "established" if the patient was kept at the breast for more than 14 days (Douglas, 1950). In the interest of brevity those in whom breast-feeding occurred for 14 days or less are referred to as "bottle-fed."

(*c*) Where the answer to the first question in the questionary was "breast-fed but duration unknown" it was assumed that breast-feeding had been established for at least 14 days.

(*d*) Where the patient's account of his infant-feeding history conflicted with that of a witness (for example, his mother) the witness's account was preferred.

Results

It will be seen from Fig. 1 that in 92 of the ulcerative colitis cases and in 110 controls breast-feeding was established, and Table I shows that in 19 patients with ulcerative colitis and in 23 controls no information could be obtained about the infant-feeding history. The vast majority of these subjects were in the older age-groups (all but eight were born before 1912), and it was possible to discard them from the analysis without interfering with the age-balance of the two groups (Table II).

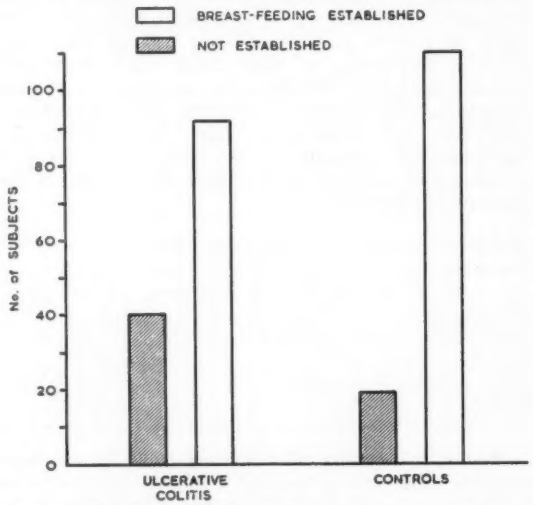

FIG. 1.—Distribution of early weaning in 132 cases of ulcerative colitis and in 129 controls in whom a history was obtainable.

TABLE I.—*Duration of Breast-feeding*

Stated Duration of Complete Breast-feeding	Ulcerative Colitis			Controls		
	First-hand Evidence	Other Evidence	All	First-hand Evidence	Other Evidence	All
Breast-feeding not established:						
0	20	4	24	7	2	9
2 weeks ..	15 } 35	1 } 5	16 } 40	8 } 15	2 } 4	10 } 19
Breast-feeding established:						
4 weeks ..	7	1	8	14	0	14
3 months ..	16	0	16	17	0	17
6 ,, ..	17	0	17	10	1	11
12 ,, ..	19 } 66	5 } 26	24 } 92	30 } 83	7 } 27	37 } 110
More than 1 year	3	1	4	4	0	4
Breast-fed, but period unknown	4	19	23	8	19	27
Total known ..	101	31	132	98	31	129
Unknown ..	—	—	19	—	—	23
Grand total ..			152			152

TABLE II.—*Breast-feeding by Year of Birth*

	-1911		1912-21		1922-31		1932+	
	U.C.	Controls	U.C.	Controls	U.C.	Controls	U.C.	Controls
Breast-feeding not established	6 (18·2)	3 (9·7)	11 (33·3)	5 (18·5)	14 (43·8)	7(17·5)	9 (26·5)	4 (12·9)
Breast-feeding established	27	28	22	22	18	33	25	27
Total	33	31	33	27	32	40	34	31
Unknown	16	19	3	3	1	1	0	0
Grand totals ..	49	50	36	30	33	41	34	31
Median year of birth ..	1904	1905	1918	1916	1926	1926	1941	1942

Figures in parentheses in this and other tables are percentages.

Of those in whom an infant-feeding history was obtained 18.2% of the ulcerative colitis patients and 7.0% of the controls had never been breast-fed ($\chi^2 = 7.42$; $0.001 < P < 0.01$) (Table I).

If those in whom breast-feeding occurred but was not established are added (that is, for 14 days or less) the difference is twofold and the proportions are 30.3% (ulcerative colitis) and 14.7% (controls). This difference is still highly significant ($\chi^2 = 9.05$; $0.001 < P < 0.005$) (Table III). A similar level of significance is obtained when only those cases in the two groups where first-hand evidence was obtained are considered ($\chi^2 = 9.90$) (Table I). If the proportions of the two groups weaned at 1 month are considered the difference largely disappears ($\chi^2 = 3.54$; $0.05 < P < 0.1$). The important difference between the groups is thus limited to the first few weeks of life.

Age and Sex.—The distribution by year of birth of patients in whom breast-feeding was not established is shown in Table II. The proportions were higher in the ulcerative colitis patients in all age-groups. This also held true for each sex considered separately. The figures also suggest that early weaning was commoner in both groups between 1912 and 1931 than it was either before or since.

Location.—The study was complicated by the fact that as a result of the department's special interest in ulcerative colitis these patients were drawn from a wider area than were the controls. For this reason the cases were divided at the outset into two groups: (*a*) those resident within the territory of the Oxford Regional Hospital Board (Group 1) ; (*b*) those from outside the region (Group 2).

Group 1 was matched with controls resident within the region and it was planned to match Group 2 with patients of similar age and sex from outside the region. In fact, only six control patients of the appropriate ages could be found from outside the region, and as the proportions of bottle-fed ulcerative colitis patients within and outside the region were closely similar (Table III) it was decided to make up the control numbers with patients from within the region. Table III shows the cases broken down into Group 1 (ulcerative colitis patients resident within the region and matched controls) and Group 2 (the remainder). Significantly higher proportions of bottle-fed patients are found among the ulcerative colitis patients in each group.

The Group 1 cases were subdivided further by residence into urban (resident in Oxford or other municipal or urban districts within the region) and rural. While the proportions of bottle-fed controls were evenly distributed in town (16.1%) and country (17.0%), in the ulcerative colitis patients early weaning seemed to be more common in country (34.7%) than in town (25.9%), but this difference could easily be due to sampling error ($\chi^2 = 0.99$; $P = 0.3$).

Social Class.—The current occupation of each patient, or in the case of women of the patient's husband, was taken as an index of social class and classified according to the Registrar-General's List (1950). In the control group the frequency of early weaning increased steeply from Social Class I to Social Class V (Table IV). A less striking trend in the same direction was seen in the ulcerative colitis patients. An excess of bottle-fed subjects occurred in the ulcerative colitis group in each social class except V, where the numbers are small and sampling error is large. The excess is less well marked in the lower social strata than in the higher. These trends are more clearly shown by compressing the data as has been done in Fig. 2.

Family Rank.—Because the length of lactation has been shown to vary slightly with the birth order of the infant (Douglas, 1950), each patient was questioned

TABLE III.—*Breast-feeding by Residence at Interview*

	Within the Region		Outside the Region		All	
	U.C.	Controls	U.C.	Controls	U.C.	Controls
Breast-feeding not established	32 (29·9)	17 (16·5)	8 (32·0)	2 (7·7)	40 (30·3)	19 (14·7)
Breast-feeding established ..	75	86	17	24	92	110
Total ..	107	103	25	26	132	129
Unknown ..	15	19	5	4	20	23
Grand total ..	122	122	30	30	152	152
	$\chi^2 = 5{\cdot}27$ $0{\cdot}02 < P < 0{\cdot}05$		$\chi^2 = 4{\cdot}78$ $0{\cdot}02 < P < 0{\cdot}05$		$\chi^2 = 9{\cdot}05$ $0{\cdot}001 < P < 0{\cdot}005$	

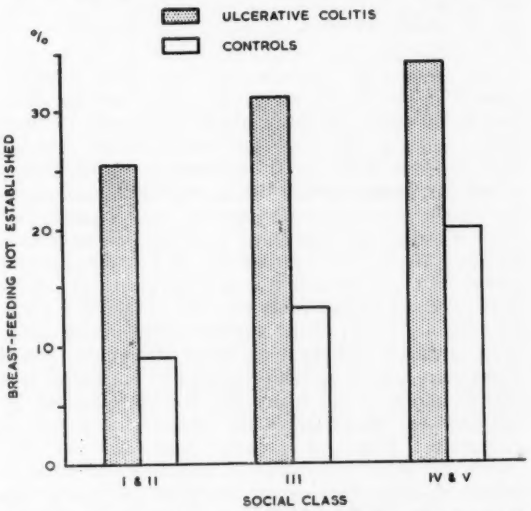

FIG. 2.—Early weaning becomes more common as the social scale descends in both groups, but is commoner in ulcerative colitis patients throughout.

TABLE IV.—*Breast-feeding by Social Class of Patient*

Breast-feeding:	Ulcerative Colitis				Controls			
	Not Established	Established	Total	Unknown	Not Established	Established	Total	Unknown
Social class I	4 (24·0)	12	16	1	0 (0·0)	8	8	1
,, ,, II	8 (25·8)	23	31	3	2 (11·7)	15	17	2
,, ,, III	19 (32·2)	40	59	8	9 (13·2)	59	68	16
,, ,, IV	7 (41·2)	10	17	3	4 (18·2)	18	22	2
,, ,, V	2 (22·2)	7	9	4	3 (25·0)	9	12	2
Total	40 (30·3)	92	132	19	18 (14·2)	109	127	23
Social class unknown ..	0	0	0	1	1	1	2	0

about his rank in the family. This inquiry was regarded as of particular interest because it has often been said (though with no reliable evidence) that ulcerative colitis is unduly frequent in "only" children. It was found, however, that the proportion of patients who had been "only" children was similar in the two groups (ulcerative colitis 8.6%, controls 9.9%). Early weaning occurred more often in every group of ulcerative colitis patients except one, when classified by family rank (Table V).

TABLE V.—*Breast-feeding by Rank of Patient in Family*

Family Rank	Ulcerative Colitis		Controls	
	Breast-feeding Not Established (%)	Total No. at Risk	Breast-feeding Not Established (%)	Total No. at Risk
1st	38·1	42	17·4	46
2nd	28·0	25	17·2	29
3rd and 4th ..	39·3	29	6·4	31
5th and more ..	16·7	36	17·4	23
Total ..	30·3	132	14·7	129

Discussion

Possible Bias in the Data

We were surprised by the high proportion of patients and their relatives who gave unequivocal answers to questions about events in the remote past. However, it would be prudent to assume that even answers readily given about the period of nursing and the date of weaning were often inaccurate. Such inaccuracies could be expected to bias the result of the survey if they acted in one direction for one group but not the other, or in inverse directions in each group concurrently. No doubt many unknown factors influenced the relationship of the answers to the truth; but two obvious ones—namely, the interval between the events and the interview and the professional relationship between the interviewer and the patient (or his relative)—were identical for both cases and controls. In addition, no knowledge of the real reason for the survey was communicated to the patient in the personal interview, and a number of other questions not concerned with infant-feeding were asked. The possibility that the interviewer (E.D.A.) influenced the answers in one or other groups is fortunately ruled out by two considerations. In the first place, the majority (74%) of the answers to the crucial questions used in the analysis came from the postal questionary, and these were classified by an independent person who was also responsible for the matching by age and sex. Secondly, in the minority in whom the information from the personal interview was used (Table I, "other evidence") the trend in favour of an excess of early weaning in ulcerative colitis was less marked than in the remainder. Short of the possible bias mentioned above, any inaccuracies about the infant-feeding histories within the survey would tend to blur rather than exaggerate the differences which were found.

A more serious possibility is that the control patients were dissimilar to the ulcerative colitis patients in some important particular with a bearing on early weaning, and that this depressed the control frequency of bottle-feeding. According to the literature, important factors which inflate the frequency of early weaning are confinement at home rather than in hospital, social factors such as overcrowding in the home, a short interval between successive births, and being the wife of a manual worker. Most of these factors are correlated with social class and are dealt with in Table IV and Fig. 2. In 1946 (*Maternity in Great Britain*, 1948) striking and unexplained differences in the early-weaning rate were found between different areas of Great Britain with comparable social conditions. For example, in that year 19% of mothers in Scotland did not start breast-feeding, as opposed to 7% in England and Wales, and there were other more local fluctuations. It is in respect of this variable that the present survey may be most open to criticism; for, in spite of the precaution taken of considering the ulcerative colitis patients from within the region separately from those outside the region, even within the region itself it was found that the ulcerative colitis patients were more likely to have come from farther afield than were the controls. However, some assurance can be gained from the fact that if the immediate area served by the Oxford United Hospitals be considered alone, early weaning was twice as common in ulcerative colitis patients (33.8%) as in controls (16.6%) ($\chi^2=6.13$; $0.01<P<0.02$). Unfortunately no help can be obtained from the literature because there are no published reports of the frequency of early weaning in the Oxford area before 1952, and even for this and subsequent years figures are given only for the frequency of breast-feeding at one and two months (Annual Report of Medical Officer of Health, Oxford, 1954). In the present study only 6% of the patients interviewed were born after the end of the second world war.

The only report dealing with infant-feeding trends in England over a long period is from Liverpool (Robinson, 1939). This study, based on large numbers of babies attending welfare clinics before the second world war, gives the percentages weaned by the end of the second week for the following years: 1918, 23.7; 1922, 25.1; 1930, 18.5; 1934, 15.7; 1937, 22.0. Even if no allowance is made for the fact that almost all of these babies were from Social Classes III–IV, the figures given are closer to those in our control group than in the ulcerative colitis group for corresponding years.

Possible Interpretations of the Findings

If the difference in the early-weaning rate found between patients with ulcerative colitis and controls is a real one, it may be interpreted in a number of different ways, but these may be classified logically into three groups.

1. A genetic or environmental influence operating in the mother *prior to weaning* in which early failure of lactation is associated with an increased susceptibility to ulcerative colitis in the child. Thus inverted nipples might be the manifestation in the mother of a gene inherited by the child which predisposed to ulcerative colitis; or breast abscess or some other early maternal illness resulting in failure of lactation might also affect the child.

2. A genetic or perinatal environmental influence operating on the infant *prior to weaning* (for example, prematurity) might prevent it from suckling and might be linked with a susceptibility to ulcerative colitis.

3. Early artificial feeding itself or an influence *resulting from it* might predispose to ulcerative colitis.

A detailed inquiry into the neonatal history of patients with ulcerative colitis is clearly the next step in unravelling these possibilities. At present the third group of possibilities seem most promising, and the most obvious of these are neonatal gastro-enteritis, psychological factors associated with deprivation of early

maternal care, and early exposure to foreign proteins. However, whatever the factor involved, it can only be expected to account for a minority of the cases of ulcerative colitis.

From a wider viewpoint, there is the interesting possibility that artificial feeding in the first few weeks of life may influence the liability to a number of diseases which occur in adult life. The ideal way to determine this would be to carry out a prospective study, but it is self-evident that the results would not be available for some decades. In the meantime the simple type of inquiry employed in the present study may be worthy of application to conditions other than ulcerative colitis.

Summary

The history of infant-feeding has been studied in 152 patients with classical ulcerative colitis and in an equal number of patients with other conditions matched for age and sex attending the Nuffield Department of Medicine during the same period. All the patients were asked a standard series of questions by the same interviewer. In 74% of the patients first-hand evidence was obtained from a witness (usually the mother) by means of a postal questionary.

It was found that breast-feeding had not been established in 30.3% of the ulcerative colitis patients and 14.7% of the controls, a difference which might occur by chance less than once in 500 times. However, when the groups were compared in terms of the proportions weaned by one month, no significant difference was apparent. When the ulcerative colitis group was compared with the control group in terms of year of birth, social class, residence at interview, and family rank a consistently higher proportion of patients who had been weaned within the first two weeks of life was found in the ulcerative colitis group.

These findings can be explained in a number of different ways, but the most likely interpretation is that early artificial feeding increases the liability to ulcerative colitis later in life. The theoretical and practical implications of this are briefly discussed.

We are indebted to Mrs. B. Hainge for matching the patients, classifying the answers to the postal questionary, and keeping the records of the study.

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The Central Council for Health Education has issued a booklet, *Helping the Elderly to Live at Home*, which is intended to serve as an introduction to some of the problems involved for relatives who care for old people at home. In addition to what may be called "clinical notes," the booklet has useful sections on making use of the social services, a list of information leaflets, references, and a list of local organizations likely to be needed by relatives, with space left for addresses and telephone numbers. (C.C.H.E., Tavistock House North, Tavistock Square, London W.C.1, price 2s.)

ASSESSMENT OF THE RADIOTRIOLEIN TEST IN STEATORRHOEA

BY

A. G. COX, M.B., Ch.B.

Research Assistant, University Department of Surgery, Royal Infirmary, Sheffield

In the investigation of steatorrhoea the fat-balance is generally regarded as the best means of assessing the severity and progress of the condition. However, there is general agreement that the fat-balance is a difficult test to conduct, and therefore alternative methods of obtaining the same information with less trouble have been proposed. One of these is the radio-iodinated triolein (RIT) test, which has received wide support in the last ten years.

Although differences in procedure are adopted by different workers, the principle employed is essentially that of a tracer test. A known dose of RIT is given by mouth, its excretion in the faeces is measured, and the result is expressed as a percentage of the dose. While quantitative agreement with the faecal chemical fat excretion is not claimed, many workers state that normal subjects excrete a low percentage of the dose, whereas patients with steatorrhoea excrete a high percentage (Ruffin *et al.*, 1956, and others). Furthermore, it is claimed that the dividing line between faecal RIT excretion in normal subjects and in patients with steatorrhoea is sharp enough to be of diagnostic value. The advantages of the RIT test are that it is easily performed, a standardized material is used, and faecal homogenization is unnecessary. Its obvious disadvantage is the possible danger inherent in the use of radioactive isotopes.

Further elaborations of the use of radio-iodinated lipids have been reported. The measurement of plasma levels of absorbed radioactivity (Berkowitz *et al.*, 1959) and the urinary excretion of ^{131}I (Walker *et al.*, 1960) have been advocated as useful parameters of intestinal function. Again, it is claimed that steatorrhoea of digestive origin can be distinguished from one of absorptive origin by comparing the absorption of RIT with that of radio-iodinated oleic acid (Reemtsma *et al.*, 1957). Finally, other workers have used these materials as a means of investigating generalized atherosclerosis (Hall *et al.*, 1959), congestive cardiac failure (Mäkelä *et al.*, 1960), diabetes mellitus (Sandberg *et al.*, 1960), cirrhosis (Fast *et al.*, 1959), the nephrotic syndrome, and other hyperlipaemic states (Stanley and Thannhauser, 1949).

Despite widespread acceptance of the method, a search of the literature reveals a paucity of critical investigations designed to assess the reliability of the RIT test in the diagnosis of steatorrhoea. Fierst *et al.* (1958) have found a correlation between the vitamin A absorption test and the RIT test. An alternative approach to this aspect of the subject is to compare the results of the RIT test with those of the standard fat balance. Although there have been many reports relating to the use of RIT, few have included this comparison (Grossman and Jordan, 1958; Lubran and Pearson, 1958; Playoust *et al.*, 1959; Pimparkar *et al.*, 1960; Vaughan Jones, 1960). This paper is a report of a further series of cases in which concurrent faecal chemical fat and faecal RIT excretion determinations were made.

Materials and Methods

Clinical Material.—100 medical and surgical patients were studied by means of a combined test in which simultaneous measurements of faecal chemical fat and faecal RIT excretion were made.

Preparation of Patient.—For two days prior to the administration of RIT each patient received a daily dietary fat intake ranging between 50 g. and 100 g.; in most the intake was 75 g. This diet continued through the period of the collection of faeces. Following the practice of Lubran and Pearson (1958), several out-patient studies were performed. These subjects received a simple diet sheet which was carefully explained. In addition, each patient received potassium iodide to block thyroidal uptake of ^{131}I.

Radiotriolein.—Of the 100 cases 82 received RIT labelled with ^{131}I as iodine monochloride by the method of Lubran and Pearson. The remaining 18 received RIT purchased from the Radiochemical Centre at Amersham. Doses were prepared by emulsification with Tween 80 and water and dispensed in a volume of 10 ml. in a glass container. Each dose was individually calibrated for radioactivity against an $Na^{131}I$ standard. The administered dose of radioactivity varied between 10 and 15 μc of ^{131}I.

Dosing Procedure.—Half the patients received their dose after a 12-hour fast and the remainder two hours after a normal breakfast. The patient drank the active emulsion direct from the dose container, which was then washed four times with water; the patient also swallowed these washings. No appreciable amount of radioactivity remained after this procedure. Immediately after the dose 250 ml. of milk was taken.

Faecal Collection.—Faeces were collected for a period of four to six days, starting with the first motion after the administration of RIT. Stools were passed direct into a rigid polythene container lined with a plastic bag. Special stress was laid on the importance of complete stool collection and on the avoidance of urinary contamination of the faeces. Where extended metabolic studies were in progress the faeces were collected between carmine markers; in patients having a regular bowel habit this was not considered necessary.

Measurements.—(i) Faecal Chemical Fat:—A sample of the total faecal homogenate was used for the determination of faecal chemical fat by the method of van de Kamer *et al.* (1949). (ii) Faecal RIT:—The total faecal collection was measured for radioactivity in a multi-tube γ-ray assay apparatus (Veall and Vetter, 1958). The containers used for faecal collection fitted into this apparatus. A solid standard was prepared in one of these containers, using a sample of the active fat emulsion or of $Na^{131}I$ of suitable activity. "Instant whip" was found to be an ideal material for making the standard solid.

In all cases the faeces were homogenized to obtain uniform dispersal of excreted RIT. In some cases the faecal specimen was also counted prior to homogenization in order to assess the necessity for this procedure. Using a counter with 10-cm. Geiger–Mueller tubes, relatively poor agreement was obtained between the pre- and post-homogenization results. When a counter with 26-cm. tubes became available the correlation was greatly improved (Fig. 1) and faecal homogenization was unnecessary with this apparatus.

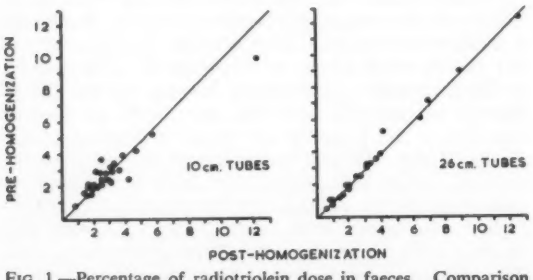

FIG. 1.—Percentage of radiotriolein dose in faeces. Comparison of the two graphs shows that agreement between the pre- and post-homogenization results is better in the counter with 26-cm. Geiger–Mueller tubes than in the counter with 10-cm. G.-M. tubes.

Results

Faecal Chemical Fat.—A daily faecal chemical fat excretion of 7 g. or more was taken as the criterion for steatorrhoea. On this basis, 67 cases were normal and the remaining 33 had steatorrhoea. The cases of steatorrhoea were analysed according to the condition causing the increase in fat excretion (Table I).

TABLE I.—*Steatorrhoea Cases*

Disease	No. of Cases
Previous gastric surgery	15
Pancreatic disease	6
Idiopathic steatorrhoea	7
Crohn's disease	3
Bile-duct obstruction	1
Carcinoma of colon	1
Total	33

Faecal RIT.—The investigation was designed to assess the reliability of the RIT test by comparing it with the results of the faecal chemical fat excretion. The results of this comparison are given graphically in Fig. 2. The faecal RIT excretion results have been divided into two groups according to the presence or absence of steatorrhoea as judged by the estimation of chemical fat (Table II).

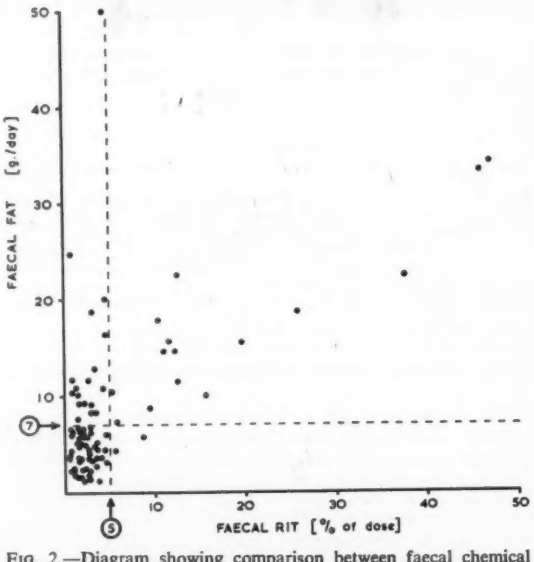

FIG. 2.—Diagram showing comparison between faecal chemical fat and faecal radiotriolein excretion in 100 cases. The broken lines indicate the upper levels of normal faecal chemical fat excretion (7 g./day) and normal faecal radiotriolein excretion (5% of administered dose).

TABLE II.—*Summary of Results of Concurrent Faecal Fat and Faecal RIT Excretion in 100 Cases*

		Cases without Steatorrhoea (67 Cases)	Cases with Steatorrhoea		
			All 33 Cases	18 Cases Faecal RIT < 5%	15 Cases Faecal RIT > 5%
Faecal chemical fat (g./day)	Mean	3·9	15·6	14·5	16·9
	S.D.	±1·4	±9·0	±10·0	±7·7
Faecal RIT (% of dose)	Mean	2·3	10·4	2·7	19·0
	S.D.	±1·3	±12·4	±1·2	±14·1

(i) *Faecal RIT Excretion in Normal Subjects.*—The 67 cases without steatorrhoea excreted between 0.6% and 8.7% of the dose of RIT. The mean was 2.3% with a statistical range of 0 to 4.9% (mean ±2 S.D.). On this basis, 5% has been taken as the upper normal limit of faecal RIT excretion. Two cases excreted over 5% (5.7% and 8.7%), results which may be regarded as "false positives."

(ii) *Faecal RIT Excretion in Cases with Steatorrhoea.*—The 33 cases with steatorrhoea excreted between 1.0% and 47.7% of the dose of RIT. Taking 5% as the upper normal limit of faecal RIT excretion, these cases can be further subdivided into two groups (Table II). Fifteen cases excreted more than 5% and were thus differentiated from the normal material. Eighteen cases excreted less than 5% and were not so differentiated; the results in these cases may be regarded as "false negatives."

Analysis of Results

The figure of 5% as the upper normal limit of faecal RIT excretion was chosen on statistical grounds. As other workers have used different values, the results were analysed to see if an alternative figure would improve the diagnostic reliability of the RIT test (Table III). Lubran and Pearson regard a range of 5–7% as equivocal, and they perform a chemical fat determination to establish the diagnosis in such cases; Vaughan Jones adopts a similar device but takes a wider range of 3–7%. In the series reported here the total number of false results is not appreciably reduced except when a range of 3–7% is taken as equivocal. In these circumstances there are only 11% of false results in the whole series, but it is important to appreciate that this figure includes an incidence of 30% of false negative results in the group of cases with steatorrhoea.

TABLE III.—*Effect of Taking Different Values for Normal Faecal RIT Excretion on the Number and Incidence of False Results*

		Faecal RIT Excretion taken as Normal (% of Dose)						
		3	4	5	6	7	Equivocal Ranges 5–7	Equivocal Ranges 3–7
67 cases without steatorrhoea	No. of false pos.	13	6	2	1	1	1	1
	% of false pos.	19%	9%	3%	2%	2%	2%	2%
33 cases with steatorrhoea	No. of false neg.	10	14	18	20	20	18	10
	% of false neg.	30%	42%	54%	60%	60%	54%	30%
100 cases in whole series	Total No. of false results	23	20	20	21	21	19	11
	% of false results	23%	20%	20%	21%	21%	19%	11%

The data on the steatorrhoea cases were examined to see if any obvious differences existed between the patients who excreted less than 5% of the RIT dose and those who excreted more than 5%. The degree of steatorrhoea was similar in both groups (Fig. 3). The other factors considered were age, sex, bowel habit, mode of faecal collection, method of administration of RIT, type of RIT, and type of steatorrhoea (Table IV). Although there are small differences, these factors do not provide an adequate explanation for the observed discrepancies, partly because of the relatively small number of cases studied.

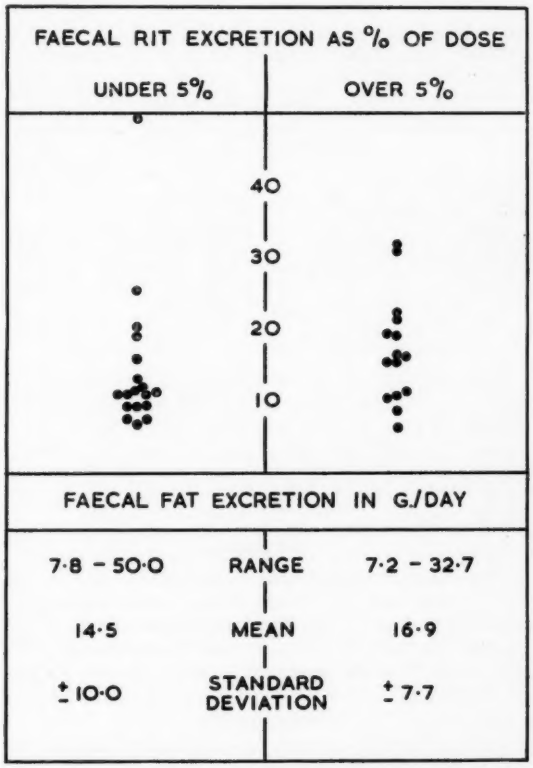

FIG. 3.—Diagram showing the faecal chemical fat excretion in the 33 cases of steatorrhoea, divided into those excreting less than 5% and those excreting more than 5% of the administered dose of radiotriolein.

TABLE IV.—*Analysis of the Two Groups of Steatorrhoea Cases*

Details of Factors Considered		33 Cases with Steatorrhoea: Faecal RIT below 5% of Dose	33 Cases with Steatorrhoea: Faecal RIT over 5% of Dose
Age (years)	Range	21–69	23–69
	Mean	45·5	50·5
Sex (No. of cases)	Male	16	9
	Female	2	6
Bowel habit (No. of motions/day)	Range	1–4	1–5
	Mean	2·0	2·5
Mode of stool collection (No. of cases)	In-patients	11	10
	Out-patients	7	5
	Between markers	3	2
	4–6 day collection	15	13
Method of dosing (No. of cases)	Fasting	9	9
	After breakfast	9	6
Type of ^{131}I Triolein (No. of cases)	Lubran and Pearson	12	13
	Amersham	6	2
Type of steatorrhoea (No. of cases)	Digestive	3	4
	Absorptive	5	5
	Gastric surgery	9	6
	Carcinoma of colon	1	0

Comparison with Similar Studies

Five studies similar to the present one have been found in the literature, and the combined results are given in Table V. This summary shows that, in a total of 391 subjects studied by concurrent measurements of faecal RIT and faecal chemical fat the RIT test gave 26% of false negative results and 6% of false positives. More recently, Lubran (1960) has found "complete agreement" between faecal chemical fat and faecal RIT excretion in 76% of a large series of cases, which included both normal subjects and cases of steatorrhoea.

TABLE V.—*Summary of Results of Six Separate Studies in Which Faecal Chemical Fat and Faecal RIT Have Been Compared*

Authors	No. of Cases		Incidence of False Results		Normal Values Adopted	
	Whole Series	With Steatorrhoea	False Neg.	False Pos.	Faecal Fat g./Day	Faecal RIT % of Dose
Grossman and Jordan (1958)	47	14	0%	0%	14·1 g.†	<5·1%
Lubran and Pearson (1958)	26	9	11%	0%	6·0 g.	5–7%
Playoust, *et al.* (1959)	48	12	0%	11%	6·5 ,,	<3%
Pimparkar *et al.* (1960)	115	54	24%	16%	7·0 ,,	<7%
Jones (1960)*	55	18	28%	5%	7·0 ,,	3–7%
Present Series	100	33	54%	3%	7·0 ,,	<5%
Totals	391	140	26%	6%		

* Complete data not yet published. † Total faecal lipids.

The present study gave the lowest success rate for the diagnosis of steatorrhoea by the RIT test, although the number of false positive results was lower than in other series. Despite the disparities between the different studies, the fact remains that several groups of workers have failed to obtain consistently reliable results with the RIT test.

Discussion

The main conclusion from this study is clearly that the test was unreliable in the diagnosis of steatorrhoea. The first section of this discussion deals with the effect of errors in stool collection on the results obtained. This is followed by a consideration of the theoretical aspects of the RIT test.

Stool Collection

In the RIT test, mistakes in faecal collection can give rise to misleading results in two ways.

Firstly, an incomplete stool collection can cause a falsely low result. This applies both to the RIT test and to the fat balance, but in the former it is a particularly important source of error. This is because most of the RIT excreted in the faeces appears in one or two motions, whereas faecal chemical fat is more evenly distributed throughout the motions passed during the test. If the motion containing the majority of the unabsorbed RIT is lost the result of the RIT test will be affected to a greater degree than the result of the chemical fat balance. This may be the cause of a "false negative" result—that is, a low faecal RIT excretion in cases with a high faecal chemical fat excretion.

The second possible source of error arises because of the urinary excretion of 50% or more of the *absorbed* radioactivity in the first two days after the administration of RIT. Therefore urinary contamination of the faeces can cause "false positive" results—that is, the appearance of a high percentage of the RIT dose in the faeces of subjects without steatorrhoea. Playoust *et al.* (1959) interpret false positive results as indicating that the RIT test is more sensitive than the fat balance in the diagnosis of steatorrhoea, but the possibility of urinary contamination as a cause of this anomaly must always be considered.

In this series, one of the false negative results could be safely ascribed to faulty stool collection, and this also seemed to be a likely explanation in a second case. If the other discrepant results were caused by errors in faecal collection, the practical value of the RIT test remains in doubt, since determined efforts were made to ensure a proper collection in every case—efforts which would not reasonably be expected in routine practice.

Theoretical Aspects of the RIT Test

Although the temptation to ascribe anomalous results to technical errors is considerable, the possibility that more fundamental errors may provide at least a partial explanation merits consideration. The validity of the RIT test rests on at least four fundamental assumptions.

(i) Validity of Faecal Measurement of RIT

The measurement of the faecal excretion of RIT is generally accepted as a valid procedure in the RIT test. While several workers have advocated plasma or urinary measurements as satisfactory alternatives, few claim that they rival the faecal determination in sensitivity. Fierst *et al.* (1958) are alone in denying the validity of faecal measurements on the grounds that excretion of iodine and iodine-containing compounds *into* the gut vitiates the results of faecal determinations.

Some evidence on this point is provided by studies in which faecal radioactivity has been measured after the parenteral administration of substances containing ^{131}I. Berson and Yalow (1954) recorded negligible radioactivity after the intravenous injection of ^{131}I as $Na^{131}I$. Van Middlesworth (1960) has shown that intravenously administered ^{113}I-labelled thyroxine is excreted in the faeces in appreciable amounts in the four days after injection. Using RIT, two groups of workers have performed similar experiments which may be expected to give the most direct evidence: in mice, Rutenburg, Seligman, and Fine (1949) found only 1% of the dose in the faeces after injection; in 5 human subjects without steatorrhoea, Lamberg *et al.* (1960) were unable to detect any faecal radioactivity in the two days following the intravenous administration of a RIT emulsion.

However unlikely Fierst's belief may appear at first sight, the question must remain open until more experimental evidence is available. This may be provided by extending the work of Lamberg and his colleagues to a study of cases with steatorrhoea.

(ii) Origin of Faecal Fat

Since RIT is used as a tracer for dietary fat, the test relies on the assumption that faecal chemical fat is derived solely from unabsorbed dietary fat. However, the origin of faecal fat is still a matter for debate (Frazer, 1959). It may be of dietary or non-dietary origin; alternatively, both sources may contribute appreciable amounts. Various sources of endogenous (that is, non-dietary) faecal fat have been suggested, including active secretion of fat into the lumen of the gut (Lewis and Partin, 1954), synthesis of fat by the bowel mucosa (Clark and Hübscher, 1960), excretion of fat in the bile (McClure *et al.*, 1934) and synthesis of fat by alimentary flora (Sammons *et al.*, 1956).

The evidence on this subject is not conclusive. Krakower (1934) and Annegers *et al.* (1948) found that alterations in the dietary fat intake in normal subjects

did not alter faecal fat output and concluded that an endogenous origin accounts for most of the faecal chemical fat in normal subjects. However, in observations on two normal subjects Wollaeger *et al.* (1953) found that faecal fat fell substantially on a lipid-free diet; their conclusion that faecal fat was mainly of dietary origin was in keeping with a previous study (Wollaeger, Comfort, and Osterberg, 1947) in which the output of faecal fat rose appreciably when the dietary intake was increased from 100 to 200 g. daily.

In patients with steatorrhoea, the general view is that faecal fat is largely of dietary origin. However, Comfort *et al.* (1953), Cooke *et al.* (1953), and Jiménez-Díaz *et al.* (1959) have reported studies in which the faecal fat output was in excess of the dietary intake. In these cases a substantial endogenous component must be accepted. In subjects studied by the RIT test a high faecal chemical fat excretion with a low faecal RIT excretion (that is, a "false negative" result) might be explained if the faecal chemical fat was chiefly of endogenous origin.

Seeking an explanation for the discrepancy between the faecal RIT excretion and chemical fat excretion in one of his cases, Jones (1960) cultured the intestinal contents in an unsuccessful attempt to repeat the work of Sammons *et al.* (1956). These workers claim to have isolated a faecal organism (from a patient with steatorrhoea) capable of synthesizing fat.

Jiménez-Díaz *et al.* (1959) used ^{131}I-labelled triolein as a tracer for dietary fat in an investigation into the origin of faecal fat. Their conclusion was that faecal fat was mainly derived from endogenous sources, both in normal subjects and in cases of steatorrhoea. Unfortunately the particular ^{131}I label used by these workers has not gained wide acceptance; furthermore, the validity of labelled triolein as a tracer material for dietary fat is a matter for further study. However, the possibility remains that, under suitable conditions, RIT may provide a useful means of assessing the dietary contribution of faecal fat, even though it may be rejected as a means of diagnosing steatorrhoea.

The answer to some of these questions might be supplied by the use of ^{14}C-labelled lipids. Unfortunately these materials are not acceptable for routine use because of the counting difficulties and because of the long half-life of the isotope.

(iii) Behaviour of RIT in the Alimentary Tract

To be acceptable as a tracer material, RIT must behave like dietary fat in the alimentary tract. Lack of evidence on this fundamental requirement is due, in large measure, to the inaccessibility of the small intestine. The assimilation of relevant data must await the development of suitable techniques. Meanwhile, RIT dosing procedures have an important practical bearing on this problem and merit further consideration.

Grossman and Jordan (1958) studied the effect of giving different fat loads with the RIT dose and concluded that the faecal RIT excretion did not vary. Similar findings have been reported by Chears *et al.* (1958). However, the latter group confined their observations to normal subjects, and Grossman and Jordan included only one case of steatorrhoea.

Playoust *et al.* (1959) have stressed the importance of determining the best dosing procedure. They reported a few cases of steatorrhoea in which the absorption of RIT was reduced by increasing the fat load given with the dose of RIT. Similar observations have been made in this department, and a series of cases is being studied with a modified dosing procedure to see if the incidence of false results can be reduced.

Of great theoretical interest is the suggestion of J. C. Charlton (personal communication, 1960) that the behaviour of RIT in the gut may be altered by the degree of saturation of the triolein molecule with the ^{131}I label. The physico-chemical properties of triolein are changed by radio-iodination, and this may be expected to have some bearing on its biological behaviour. However, it is known from experience that the same batch of RIT may successfully diagnose steatorrhoea in one case and yet fail in another. Therefore it seems unlikely that Charlton's theory will provide a complete explanation of the false results.

(iv) Stability of the RIT Bond

The assumption is generally made that the radio-iodinated triolein bond is stable in the alimentary tract. If this assumption proves to be incorrect and a substantial amount of the ^{131}I label is split off within the lumen of the gut, the RIT test is vitiated, since the metabolic pathway of iodine differs from that of fat.

Turner (1958) has conducted an extensive series of experiments which rely on the observation that the circulating radioactivity of absorbed RIT exists partly as lipid-bound ^{131}I and partly as unbound ^{131}I, liberated from the RIT bond. This observation has been confirmed by many workers. Van Handel and Zilversmit (1958) gave ^{131}I-labelled fat and unlabelled fat simultaneously to dogs and rats, and showed that the plasma and lymph concentrations of the labelled fat were lower than those of the unlabelled fat, and that some of the circulating ^{131}I was not lipid-bound. In the same study they found that ^{14}C-labelled fats behaved in the same way as the unlabelled fats. The anomalous behaviour of RIT was ascribed to liberation of the ^{131}I label either in the lumen of the gut or in the mucosal cells.

The exact site of liberation of the ^{131}I label remains uncertain. Most authors favour the suggestion that this occurs in the mucosal cells of the alimentary tract, and this is supported by the *in vitro* tests of Balint *et al.* (1960), in which appreciable liberation of free ^{131}I occurred when RIT was incubated in extracts of intestinal mucosa. Similar experiments by the same workers, and by Beres *et al.* (1957), failed to detect free ^{131}I when RIT was incubated in a variety of intestinal secretions; however, their periods of incubation were relatively short. The use of an anion exchange resin to determine free ^{131}I in radio-iodinated lipids offered a simple means of studying the behaviour of the RIT bond over a longer period of time. Using this method, the most striking finding was a steady rise in the amount of free ^{131}I when RIT was incubated in human duodenal juice over a period of four days (Cox and Hinchliffe, 1961). This appeared to be due to the enzymes, because free ^{131}I was not detected when the incubation medium was *boiled* duodenal juice. Since the lipolytic activity of duodenal juice falls off very rapidly *in vitro* (Lagerlöf, 1942), its bond-splitting potency may be less in laboratory experiments than in the alimentary tract. The possibility that the RIT bond is appreciably unstable under the conditions of the RIT test remains to be explored by *in vivo* experiments.

Summary

The value of radiotriolein in the diagnosis of steatorrhoea was assessed in 100 subjects by comparing the faecal radiotriolein excretion with concurrent faecal chemical fat determinations.

Sixty-seven cases did not have steatorrhoea as judged by a faecal chemical fat excretion below 7 g. daily. In these the upper limit of faecal radiotriolein excretion was 5% of the administered dose.

Thirty-three cases had steatorrhoea as judged by the faecal chemical fat excretion. Of these, 15 excreted more than 5% of the dose of radiotriolein. The remaining 18 excreted less than 5% and were not differentiated from the normal material.

Analysis of these results failed to explain the discrepancies. Comparison with similar studies has shown that some other workers have also found the radiotriolein test to be unreliable in the diagnosis of steatorrhoea.

If technical errors are the explanation of the false results, the practical value of the radiotriolein test is lessened.

Several possible defects and a few alternative applications of the radiotriolein test are discussed.

This study was assisted by the Tuberculosis Research Fund of the University of Sheffield. I am indebted to Professor A. W. Kay for invaluable advice and encouragement throughout; to the following consultants for allowing me to study their patients: Dr. H. P. Brody, Dr. C. E. Davies, Mr. F. J. P. O'Gorman, Dr. E. G. G. Rhind, Dr. E. W. Skipper, and Professor G. M. Wilson; to Dr. A. Jordan for faecal chemical fat determinations performed in his department; to Mrs. O. Fisher for guidance in radioisotope techniques; to Messrs. A. Bird and Sons Ltd. for supplies of "instant whip"; and to Miss R. Chalmers and Miss Z. Hinchliffe for technical assistance.

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Medical Memoranda

Perforated Peptic Ulcer in Late Pregnancy

Peptic ulcer rarely occurs in pregnancy. This had probably been known to the astute physician since time immemorial, but Avery Jones's (1947) figures came to most as a surprise. He was unable to find a single case of peptic ulcer occurring among 10,000 pregnancies and 2,000 abortions reviewed. If peptic ulcer is rare, complications of peptic ulcer are, not unnaturally, exceedingly rare, and when Sandweiss *et al.* (1943) reviewed the world literature they were able to find only 13 recorded cases of complications of peptic ulcer occurring during pregnancy—nine perforations and four haemorrhages.

In this country two cases of perforated peptic ulcer in late pregnancy have been recorded during the past 13 years. James's (1948) case occurred at the 36th week, and ended satisfactorily for mother and child. The perforation was repaired, and the mother was delivered of a live child four days later. Both did well. Ten years later a case was described by Horwich (1958), occurring in the 32nd week. Conservative treatment was adopted, but this was not successful, a stillborn child being born the following day. Laparotomy was eventually necessary 60 hours after the onset of the perforation. The perforation was sutured, and after a very stormy convalescence the patient recovered.

The present case, in which twins were born the day after a partial gastrectomy, would appear to be unique.

Case History

A married woman, aged 38, and 31 weeks pregnant, was admitted to the Maternity Department of Upton Hospital on January 7, 1961, as a case of suspected hyperemesis gravidarum. She had been vomiting persistently for three weeks, prior to which the pregnancy had been normal. A year previously she had had some abdominal pain, for which she had taken medicine; but she was not a known case of peptic ulcer, though there was a family history of it. In the early hours of the morning following her admission she began to complain of severe abdominal pain, and Dr. Ralph Evans, the house-surgeon, wisely suspected the possibility of a perforated peptic ulcer. When I saw

her she was extremely ill. She was only semiconscious, and looked toxic and dehydrated. A rigid and retracted epigastrium brought her large uterus into grotesque relief. There was little doubt regarding the diagnosis, and this was confirmed radiologically. At operation she was found to have an enormous perforation of such an extensive duodenal ulcer that I was in no doubt whatever that the correct procedure was a partial gastrectomy. Despite limited exposure and a horrid duodenum, the operation was not difficult. This was doubtless due to the excellence of my anaesthetist and assistant, but I should like to recommend very strongly a left-sided stance when faced with mobilization of a difficult duodenum: this is the only difficult step in any partial gastrectomy, and I always do these cases from the left, just as one stands on the right when mobilizing a spleen. Perhaps with me there is the added feature of familiarity. Having spent so many years standing on the left to assist other surgeons to do gastrectomies, one tends to remain there, like the cat who remains on the hearth even when the fire has gone out.

The patient went into labour next morning, and was delivered of live twins. Unfortunately one of these died, but the other survived. The patient herself made a quick recovery, and in less than a week was up and about and eating an almost normal diet. She remained in hospital a further two weeks, but this was only because she had no immediate home to which to go. Her rapid recovery was perhaps partly due to the natural resilience of pregnancy and partly to the patient's innate toughness—she was a native of the Shetland Islands !

I should like to thank Mr. Tom Ealand, under whose care the case was admitted, and Dr. Kimmet for an excellent anaesthetic in rather trying circumstances.

Robin Burkitt, M.A., M.D., F.R.C.S., F.R.C.S.I.,
Upton Hospital, Slough.

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Home-made Wine as a Cause of Lead-poisoning : Report of Case

Wine-making at home is a hobby enjoying a revived popularity and there are quite a number of publications on this subject. In these, details and advice are given on the container to be used for the fermentation, and from time to time one finds the reader encouraged to seek out in antique or junk shops large old crocks, which are regarded as being eminently suitable for the brew. However, it has been shown by Prior and Whitehead (1960) that some of these aged vessels are highly dangerous owing to the high lead content of their interior glazing, and an account is given here of another case of severe lead-poisoning from this cause. Although this is an uncommon cause of lead-poisoning in this country, it is still regarded as a serious problem in other countries (Beritić and Stahuljak, 1961).

Case Report

The patient, a gardener aged 52, was admitted to hospital as a surgical abdominal emergency, ? intestinal obstruction. He gave a history of loss of appetite for one month and constipation for one week before admission. He had vomited a few times during the three days before we saw him, and had then developed some colicky lower-abdominal pain.

On examination he was rather dull and listless, and said he felt weak. Temperature 99° F. (37.2° C.). Pulse 100. Tongue dry and furred. Gums showed no significant abnormality. Abdomen very obese, tenderness in the right iliac fossa and centrally. Liver and spleen not palpable. Rectal examination negative. Blood-pressure 140/80. Heart normal. The other systems were clinically normal.

It was decided to prepare the patient for operation for possible intestinal obstruction as a straight *x*-ray film of the abdomen was thought to suggest small-bowel obstruction. However, a routine blood count showed: haemoglobin, 62% (9.05 g./100 ml.); white blood count, 13,000/c.mm. (polymorphs 68%, lymphocytes 26%, monocytes 6%). Film: the red cells showed anisocytosis and marked polychromasia and punctate basophilia; some late normoblasts were seen. The blood picture was very suggestive of a haemolytic anaemia. Further investigations showed: direct Coombs test negative; red cells negative for the presence of Heinz bodies; red-cell fragility within normal limits; serum bilirubin 1.9 mg./100 ml.; E.S.R. 12 mm. in 1 hour.

The possibility that this might be a case of lead-poisoning was discussed with the surgeons, and the operation was postponed while further investigations were carried out. The patient would not admit to having used or been in contact with any lead-containing compounds in his work or elsewhere, and at this time only admitted to moderate drinking of draught cider (proprietary brands, not home-made). The urine gave strongly positive qualitative tests for both coproporphyrins and uroporphyrin. A specimen of urine submitted for lead content was found to contain 0.3 mg./litre—that is, about ten times the quantity normally present in unexposed persons, and the amount found in persons with clinical symptoms of lead-poisoning.

A firm diagnosis of lead-poisoning was now made, and treatment with calcium disodium versenate was begun, 2 g. daily for seven days. A more intensive search was made for the source of the lead, but investigation of garden sprays used by the patient, greenhouse paint, domestic water and garden standpipe water, and cider from the draught-cider cask all proved negative for any significant amounts of lead. The patient responded well to treatment, and three weeks after admission his haemoglobin had risen to 86%, though the red cells still showed some punctate basophilia. He was symptom-free and much brighter. On being questioned once more with regard to his habits and hobbies he mentioned the fact that he made wine at home, but denied using a lead-containing vessel. However, as he was ready for discharge, arrangements were made to obtain some of the remains of the wine which he had been drinking, and also to examine the container he had used for the brew.

The wine he had been drinking for some time before his admission to hospital was damson wine prepared by himself more than a year before his admission to hospital. He had made 5 gallons (22.8 litres) of this wine and had consumed nearly all of it in the months before his admission, at the rate of 2–3 pints (1.1–1.7 litres) a week. Fortunately he had a little wine and sediment left in one bottle, so a sample of this was analysed for lead content. If there had been any doubts about the diagnosis, these were certainly dispelled by finding a concentration of 120 mg./litre.

The wine had been prepared in a large old bread crock which had been given to him by his employer, in whose family's possession it had been for at least 70 years. The fruit had been placed in the crock and then covered with boiling water. It was then left for ten days, after which the liquor was separated and replaced in the crock, then sugar and yeast were added, and the whole brew was allowed to ferment for about two to three months. After completion of the fermentation it was bottled.

The patient was informed of our findings and advised not to use this crock again for wine-making and wisely broke the crock up, but, unfortunately, before we had had an opportunity to examine it whole; however, we managed to obtain a few pieces. Some of the glaze was scraped off these and the scrapings were placed in very dilute hydrochloric acid at 37° C. overnight. The resultant solution gave very strong standard analytical tests for lead. The crock

had been used for preparing some dandelion wine before the damson wine was made; but this had been done without the addition of boiling water, and flower wines are a good deal less acid than those prepared from fruits—usually acid in the form of lemon juice has to be added.

The man has made a full and complete recovery, and when seen recently his haemoglobin was 106% (15.48 g./100 ml.) with a normal blood film. He told us that a number of his wine-making friends, who also had used old earthenware containers, had got rid of them on hearing of his illness.

Comment

Many earthenware vessels made in this country prior to this century were lead-glazed and had a very appreciable lead content (Prior and Whitehead, 1960); even to-day, on the Continent, as pointed out by Beritić and Stahuljak (1961), earthenware pots or jugs are still made with lead glazing. It is therefore hazardous to use either old glazed earthenware vessels or, possibly, even those of more recent manufacture, particularly if foreign in origin, for wine-making. Those who indulge in this pleasant and absorbing hobby would be well advised to use glass or plastic containers, which we have found very suitable for this purpose.

Our thanks are due to Dr. A. I. G. McLaughlin, of the department for research in industrial medicine, London Hospital, for the lead tests on the urine and wine.

C. Rickword Lane, D.M., D.P.H.,
A. Lawrence, M.B., Ch.B.,
Group Laboratory, St. Luke's Hospital, Guildford, Surrey.

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A Case of Massive Gas Gangrene

Gas gangrene is a rarity in civilian practice. In military spheres the principle of wide surgical excision of necrotic tissue, coupled with the use of antitoxin and antibiotics, has so reduced the incidence that in the second half of the Korean War only four cases of gas gangrene, none of them fatal, were reported in 4,900 casualties (Howard and Inui, 1954).

The following case of massive gas gangrene of the thigh complicating a previously symptomless diverticulitis of the pelvic colon, is rare enough to merit recording. Although a similar condition was treated with leeches in 1908, the mode of presentation adds interest to this case (Dawson and Hardy, 1948).

Case Report

A 70-year-old man who worked at Whipsnade Zoo was referred to the Luton and Dunstable Hospital by his general practitioner for an orthopaedic opinion on the cause of his sciatic pain. A month previously he had fallen from his bicycle and hurt his left hip. Initially this had caused him little discomfort, but after 10 days the pain became worse and radiated down the back of the thigh to the left ankle. Because of this pain distribution he was treated for sciatica with bed rest and analgesics. After a further three weeks the pain had become so intense that he could not walk. During this period an enema relieved his constipation of four days' duration. He gave no history of abnormality of bowel habit save for mild constipation easily controlled by simple laxatives.

On admission he was slightly jaundiced, at times irrational, and extremely depressed. He complained of great pain when any attempt was made to move him. His mucous membranes were pale and his tongue was furred but moist; no abnormalities of the cardiovascular or respiratory system were found. His abdomen was very distended and hyperresonant with increased bowel sounds. A left reducible direct inguinal hernia was present. The left leg showed gross pitting oedema from the ankle to the groin. The thigh and especially the groin were extremely tender. His urine contained bile pigment and urobilinogen in excess. Serum chemistry showed an alkaline phosphatase of 17 K-A units; blood urea, 77 mg./100 ml.; sodium, 300 mg./100 ml.; potassium, 17 mg./100 ml.; chloride, 540 mg./100 ml.

Because of his cachectic appearance, his jaundice, and the distribution of his pain, *x*-ray films of the lumbar vertebrae were taken to exclude neoplastic secondary deposits in the spine. The vertebrae, however, were obscured by intestinal gas shadows.

A presumptive diagnosis of iliac vein thrombosis secondary to carcinomatosis and general debility was made.

The patient passed flatus but had no bowel action. The next day he was still desperately ill and a reassessment of the original *x*-ray films was made. In the antero-posterior view of the left hip a small area of translucency, suggestive of gas, was noted in the muscle bellies on the medial side of the thigh and was just visible on the edge of the film. A soft-tissue *x*-ray film was then taken which showed extensive areas of gas tracking down the thigh and appearing to originate from the left inguinal region. Superiorly they extended above the level of the greater trochanter and inferiorly to some 4 in. (10 cm.) above the knee. A diagnosis of massive gas gangrene of the thigh was made and 30,000 units of mixed antitoxin and 1 mega unit of penicillin were given and repeated six-hourly. Thirty-six hours after admission the gas had tracked along the more superficial tissue planes and crepitus was detectable in the left groin.

As soon as the diagnosis was established the thigh was widely incised and widespread muscle necrosis was found. The mucle bellies were a pale yellowish colour and they emitted the typical aroma of gas gangrene. Because the gangrene extended above the trochanter amputation was not performed. The wound was left open and hydrogen peroxide packs were applied. Laparotomy through a left paramedian incision showed the liver to be uniformly enlarged, but no other gross disease was noted. A swab of the thigh taken at operation and cultured anaerobically grew *Clostridium welchii*.

Intravenous fluids, including 20% dextrose, were given and penicillin and antitoxins continued, but the patient died 62 hours after operation.

The findings at necropsy were diverticulitis of the pelvic colon giving rise to a pericolic abscess which had tracked into the thigh along the line of the psoas muscle. A small inguinal hernial sac containing a knuckle of viable small bowel was noted. From this abscess track in the thigh the gas gangrene had involved the related muscles and had spread superiorly to the glutei.

Comment

Two other cases have been reported, one presenting with a painful leg and swelling in the groin, and the other with a groin abscess (Dawson and Hardy, 1948). The development of a psoas abscess appears to be a common feature of these three cases.

Although gas gangrene has been noted as a complication of diverticulitis, development of massive gas gangrene of the thigh must remain a very rare presenting feature of this condition.

I thank Mr. L. W. Plewes for his encouragement and permission to write this report.

J. B. Nichols, M.B., B.Chir., D.Obst.R.C.O.G.,
Late House-surgeon, Luton and Dunstable Hospital.

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Reviews

MULTIPLE SCLEROSIS AND DIETARY FAT

A Biochemical Basis of Multiple Sclerosis. By Roy L. Swank, M.D., Ph.D. (Pp. 88+ix. 40s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Since no single link in the chain of causation which culminates in the gliotic and demyelinated plaque of multiple sclerosis is clearly understood no hypothesis can be ignored, and we must be grateful to Professor Swank for defining his very personal view of the disease within the slender compass of a new volume in the American Lecture Series. The hypothesis put forward has taken shape in more than a score of papers published during the past dozen years, and may be summarized as follows: in a very small number of people constitutionally susceptible to multiple sclerosis a high intake of dietary fat causes adhesiveness of red blood cells, slowing of the circulation, capillary embolism, tissue hypoxia, and the escape of myelinolytic substances into the brain through a damaged blood–brain barrier.

This theory rests on the perivascular distribution of the initial lesion of multiple sclerosis, on clinical evidences of vascular involvement in the disease, and on epidemiological observations. The author regards multiple sclerosis as essentially a disease of modern times and of Western civilization, and is satisfied by the suggestive evidence of its increasing prevalence. He relates its predilection for colder climates and higher social groups to consumption of fat, and suggests that common dietary habits may also contribute to its familial incidence. He goes on to demonstrate the clinical benefit which he has observed from the use of a low-fat diet in the treatment of the established disease.

In fairness to Dr. Swank he stresses the tentative nature of his formulation and invites criticism. The attractions of his hypothesis are obvious—and objections legion. The first concerns the epidemiological observations which constitute the *leit-motiv* of his contributions. Before neurologists will join their cardiological colleagues in attempting to bankrupt the dairy industry—and modestly correcting dietary habits of several thousand years' standing—they will need more convincing evidence that the differential geographical incidence both of multiple sclerosis and atheroma is not due to Protestantism, central heating, spirit-drinking, woollen underwear, or some parallel concomitant of life in a cold climate. Plotted against the prevalence of multiple sclerosis, several of these factors could yield a curve very similar to that on p. 35, where a "theoretical relationship of prevalence of multiple sclerosis to intake of animal and butterfat" is elegantly demonstrated—and thereafter endowed with causal significance.

The author's review of vascular phenomena in multiple sclerosis (chapter IV) is both selective and uncritical, and he seeks support for his case in isolated observations of dubious authenticity. His account of factors which influence the severity of the disease (chapter V) rests entirely on clinical impression. The statement that "spinal punctures and myelograms . . . are poorly tolerated and should be avoided," for example, flatly contradicts the only controlled observations which have been made on the subject. Again, to say that the infrequency of conjugal cases would "appear to automatically rule out infection as a cause of multiple sclerosis" fails to consider the quite distinct possibility that an initial infective factor might operate only in early life: after all, husband and wife do not commonly catch mitral stenosis from one another.

But it is in the therapeutic observations of chapter VI that uneasy suspicions crystallize into virtual certainty that the author is riding a hobby-horse rather than dispassionately seeking the truth. It is enough to say that the claims Professor Swank makes for the beneficial effects of a low-fat diet would satisfy only the Russian proponents of the multiple sclerosis vaccine. Like him, they also observed outstanding benefit in the earliest cases and a striking lack of response in patients with the chronic disease. He shares with them an apparently blissful unawareness that the evaluation of therapy in a chronic remitting disease demands the most scrupulously controlled observations if it is to have any meaning at all.

The book contains some unusual examples of modern English usage. The "perimeters" of vascular phenomena are twice studied, the "affect" of climate on multiple sclerosis is critically discussed, and a history is "illicited" (under what intriguing circumstances, one wonders). But all this and more we probably owe merely to an epidemic of careless proof-reading. The connoisseur in these matters need have no such half-hearted reservations about Dr. Newton Kugelmass's brief and jewelled foreword, from which he will learn with relief that the "nisus elan" of this series of lectures is happily guaranteed by an adequate supply of "key hybrid investigators."

HENRY MILLER.

MIDWIFERY TEXTBOOK

A Textbook of Midwifery. For Students and Practitioners. By R. W. Johnstone, C.B.E., M.A., M.D., Hon.LL.D., F.R.C.S.E., F.R.C.O.G., F.R.S.E. Eighteenth edition. Revised in collaboration with R. J. Kellar, M.B.E., M.B., Ch.B., F.R.C.S.E., F.R.C.P.E., F.R.C.O.G., F.R.S.E. (Pp. 592+xvi; illustrated. 45s.) London: Adam and Charles Black. 1961.

How pleasing it is to see that this new edition of a 48-year-old textbook is still partly the work of the original author. He deserves congratulations on the continued health, vigour, and youthful outlook which make this possible. For midwifery has changed radically, even since Professor Johnstone's retirement from active practice. Yet this edition presents a modern, if properly conservative, approach to the subject; so the book remains one of the best of its kind for undergraduates and general practitioners. It is comprehensive without being too detailed, and gives the reader information in such a simple and systematic manner as to make remembering it relatively easy. There is new material throughout but mainly in the chapters dealing with toxaemia, forceps delivery, and obstetric radiography.

I have always particularly liked the basic sections—such as those dealing with the development of the placenta, the normal and abnormal pelvis, the diagnosis of pregnancy, and the mechanisms of labour. In general, however, this work is appropriately stronger on the practical than on the theoretical aspects of obstetrics. As a standard textbook, it will, like its predecessors, find a host of satisfied readers. Students, however, need to be wary of the authors' use of the label "achalasia of the cervix" to mean incompetence of the cervical sphincter mechanism such as can cause abortion and

premature labour. According to my reference book achalasia has an opposite meaning—namely, failure to relax. And this is the sense in which the term has hitherto been used in relation to the cervix, and indeed to other organs in the body.

T. N. A. JEFFCOATE.

ANATOMY OF VISUAL SYSTEM

System of Ophthalmology. Volume II: *The Anatomy of the Visual System.* By Sir Stewart Duke-Elder, G.C.V.O., F.R.S., and Kenneth C. Wybar, B.Sc., M.D., Ch.M., F.R.C.S. (Pp. 901+xxii; illustrated. £6 10s.) London: Henry Kimpton. 1961.

World ophthalmology has for long been the recipient of outstanding publications, be they books or original papers, from this remarkable author. His *Texbook of Ophthalmology,* comprising six volumes, each of some 800 pages, earned universal admiration as each volume appeared during the past quarter-century, for the magnitude of this work is matched only by the quality of the contents and the excellent English in which it is written. One Continental ophthalmologist remarked that one Scotsman had produced a book which 20 Germans could not have compiled between them. It was the first great textbook of ophthalmology from a British author.

The *System of Ophthalmology* is conceived on the same grand scale, revising and bringing up to date the earlier work. In Volume II, *The Anatomy of the Visual System,* Kenneth Wybar has collaborated. It might seem that anatomy is one aspect of the specialty which would scarcely change in a generation, but in fact much detail has been added to our knowledge. The work of Norman Ashton at the Institute of Ophthalmology on the histology of the structures around the angle of the anterior chamber and the canal of Schlemm has improved our understanding of the causes of many types of glaucoma, though the problem of chronic simple glaucoma is still unsolved. Our knowledge of the visual pathways and the higher visual centres has increased, and the electron microscope has opened a new phase in the study of cell structure.

Surprising as it may seem, *The Anatomy of the Visual System* now occupies about the same 850 pages and 850 illustrations which anatomy and physiology together required in 1930. There cannot be the slightest doubt that this new work will have as great an appeal as its predecessor, which is to be found in every ophthalmic centre throughout the world. This volume is a portion of another indispensable textbook for which this country is both grateful and proud.

HAROLD RIDLEY.

RADIATION PROTECTION

Protection Against Radiation. A Practical Handbook. By John D. Abbatt, M.B., Ch.B., D.M.R., J. R. A. Lakey, Ph.D., B.Sc., A.Inst.P., and D. J. Mathias. Foreword by J. S. Mitchell, C.B.E., M.A., M.D., F.R.C.P., F.F.R., D.M.R., F.R.S. (Pp. 235+viii; illustrated. 25s.) London: Cassell. 1961.

Safety officers in works employing personnel exposed to ionizing radiations have very important duties. The final responsibilities for such protection lie in teamwork of physicists and medical men with full specialized knowledge. In this book the authors have attempted to present information which is available to-day in order to guide those responsible for the care of workers exposed to such radiations. A brief summary of biological effects is given, because protection implies the steps necessary in order to avoid these effects. Physics, background radiations, units of radiation, and detection and detectors are clearly summarized in order to understand and appreciate their action. The significance of radiation exposure in relation to absorbed dose and the resultant biological effect, methods of shielding, techniques of personal protection, and working conditions precede the final chapter on the treatment of radiation effects.

Such is the scope of the book. It succeeds in presenting this account of a vast range of medical and scientific disciplines in a clear, concise, and interesting form.

I. G. WILLIAMS.

GYNAECOLOGICAL UROLOGY

Gynäkologische Urologie. By W. Langreder. Foreword by Professor Dr. H. Schwalm. (Pp. 306+xii; illustrated. DM. 59.) Stuttgart: Georg Thieme Verlag. 1961.

Urinary symptoms are an integral accompaniment of many gynaecological diseases, and a working knowledge of general urology is an essential for every gynaecologist. It is, however, often tedious and time-consuming to pick out the appropriate information from a standard urological textbook, and the present work, which is concerned mainly with the overlapping fields of the two specialties, is particularly welcome.

Written by a gynaecological surgeon, the book is exceptional in being directed mainly to the specialist in this subject, emphasis being laid throughout on the clinical gynaecological aspects of most of the conditions described. At the same time the anatomical and physiological bases of normal and abnormal micturition are described in detail, and the chapters on functional anatomy and pathology take up a substantial part of the book. The changes in the urinary tract associated with pregnancy are particularly well described, and those secondary to uterine prolapse are illustrated in a manner at once simple and comprehensive. Indeed, the whole work is exceptional in the clarity of its text, which is succinct without compression, and comprehensive without prolixity. The many diagrammatic illustrations are beautifully drawn and appropriate to their subject, and the three indexes at the end are a model of easy cross-reference. The book is excellently printed and produced, and will no doubt become the indispensable vade-mecum of many practising gynaecologists.

ALBERT DAVIS.

NORMAL SKULL VARIATIONS

The Normal Skull. A Roentgen Study. By Robert Shapiro, M.D., and Arnold H. Janzen, M.D. (Pp. 257+ix; illustrated. No price.) New York: Paul B. Hoeber, Inc. 1960.

Radiological methods have contributed materially to knowledge of human structure and function. The appreciation of anatomical structure in radiographic work is similarly of great importance to the practising radiologist and is shown to excellent advantage in this well-produced book; its 645 illustrations are mostly composed of clearly reproduced and annotated radiographs. From their experience in practice and in teaching the authors realized that there is an unfamiliarity with the wide range of variability of the normal human skull. In demonstrating this variability, and the radiographic appearance of common anomalies and changes due to age, and by concentrating upon such details as the sella turcica, sutures, cranial mensuration, physiological calcification, and paranasal sinuses, the authors have succeeded in their task. There are also

sections upon the vascular supply of the skull and intracranial structures, the ear, mastoid, and petrous temporal bone. An outline of techniques, and a summary of the relevant development and conventional anatomy, precede the sections on radiological anatomy. The quality of publication is excellent, and the overall result a valuable monograph to the otorhinolaryngologist, neurologist, and anatomist, as well as to the radiologist.

R. G. Harrison.

OLD AGE IN AUSTRALIA

Growing Old. Problems of Old Age in the Australian Community. Edited by Alan Stoller. (Pp. 205+ix. 15s.) Melbourne: F. W. Cheshire, for the Victorian Council for Mental Hygiene. 1961.

This is an account of a seminar held in June, 1958, and sponsored by the Council for Mental Hygiene in the State of Victoria, Australia, to promote the welfare of the aged. The subject is, therefore, dealt with more from the psychiatric viewpoint than any other, and the chapters on the physical and medical aspects of the problem of growing old scarcely justify their titles. However, the causes and prevention of mental ill-health are well and fully examined. Readers in Great Britain may not discover much here that is new, but it is interesting to find that when the Australian community examines its emerging geriatric problem for itself it discovers just the same difficulties as are met here, and proposes very similar solutions.

The first half of the book consists of thirteen prepared papers on the social, legal, economic, employment, educational, and spiritual needs of elderly people, and on the psychiatric disorders of old age. These form the basis of discussion and are a valuable contribution. The second half records the five sessions of discussion themselves, and here the book is less successful. The titles of the discussions were different but the matter was much the same in each: some speakers tended to pose problems in a series of rhetorical questions which remained largely unanswered. There has been editing of the verbatim reports, but it could have been done more drastically. Indeed, the real value of the modern trend towards publishing the complete discussions of symposia, including even chairmen's interjections, in book form is open to question. Nevertheless, this pleasantly produced short book will be valuable to medical, social, and other workers in the community it has considered, and to others elsewhere who are interested in comparisons.

J. N. Agate.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Clinical Application of Antibiotics. Vol. II. By M. E. Florey, M.D. (Pp. 336; illustrated. 84s.) London, New York, Toronto: Oxford University Press. 1961.

Freud and Psycho-Analysis. Vol. IV of Collected Works of C. G. Jung. Edited by Sir Herbert Read, Michael Fordham, M.D., M.R.C.P., and Gerhard Adler, Ph.D. Translated from the German by R. F. C. Hull. (Pp. 375. 37s. 6d.) London: Routledge and Kegan Paul. 1961.

Principles of Medical Statistics. Seventh Edition. By Bradford Hill, C.B.E., D.Sc., Ph.D., F.R.S. (Pp. 367+ix; illustrated.) London: The Lancet Ltd. 1961.

Science Survey 2. Edited by A. W. Haslett and John St. John. (Pp. 372; illustrated. 30s.) London: Vista Books. 1961.

European Conference on Microcirculation. Edited by H. Harder. (Pp. 426+x; illustrated. Sw. fr. 65.) Basle, New York: S. Karger. 1961.

Progress in Surgery. Vol. I. Edited by M. Allgower. (Pp. 225+xvi; illustrated. Sw. fr. 54.) Basle, New York: S. Karger. 1961.

Duodenal Ulcer and Other Gastro-Intestinal Conditions. By Sir Adolphe Abrahams, O.B.E., M.D., F.R.C.P. (Pp. 127+vii. 12s. 6d.) London: Elek Books Ltd. 1961.

Municipal Composting. By A. G. Davies. (Pp. 203; illustrated. 30s.) London: Faber and Faber. 1961.

Central Sterile Supply. Edited by Brian Watkin, S.R.N., B.Sc. (Econ.). (Pp. 58. 4s. 6d.) London: Macmillan and Co. Ltd. 1961.

Ageing and the Semi-skilled: A Survey in Manufacturing Industry on Merseyside. Medical Research Council Memorandum No. 40. By Alastair Heron and Sheila M. Chown, assisted by M. S. Featherstone and Catherine M. Cunningham. (Pp. 59+viii; illustrated. 5s.) London: H.M.S. Office. 1961.

Human Anatomy for Art Students. By S. Tresilian and Herbert F. Williams, F.R.P.S. (Pp. 112; illustrated. 35s.) London: Chapman and Hall Ltd. 1961.

Problems in Etiology, Pathogenesis, and the Early Diagnosis of Cancer and Pre-Cancerous Ailments of the Stomach. By K. A. Skulme. Translated from the Russian. (Pp. 441; illustrated. 70s.) Riga: Academy of Sciences of the Latvian S.S.R. Jerusalem: Program for Scientific Translations. 1961.

La Sénescence Prématurée et ses Traitements. By L. F. Fichez and A. Klotz. (Pp. 166+vi+4-page supplement. 15 NF.) Vienna: Editions FIR. 1961.

New Communities in Britain. Achievements and Problems. By J. H. Nicholson. (Pp. 191; illustrated. 10s. 6d.) London: The National Council of Social Service, Inc. 1961.

The Achievement of Soviet Medicine. By L. Fridland, M.D. Edited by W. Horsley Gantt, M.D. (Pp. 352. 35s.) London: Vision Press Ltd. 1961.

Gynaecology for Students. By Lance Townsend, M.D., B.S., F.R.C.S.(Edin.), F.R.A.C.S., F.R.C.O.G., D.T.M.&H. (Pp. 331; illustrated. 63s.) Melbourne: Melbourne University Press. London: Cambridge University Press. 1961.

Looking After Your Baby. By J. A. Waycott, M.B., M.R.C.P., D.C.H. (Pp. 90. 4s.) London: W. and G. Foyle Ltd. 1961.

Family Spending Patterns and Health Care. By H. Ashley Weeks. (Pp. 140+vi; illustrated. 28s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1961.

A Guide to Dental Therapeutics. By J. C. Macdougall, L.R.C.P., L.R.C.S., H.D.D., L.D.S., and George S. Nixon, Ph.D., F.D.S., H.D.D., L.D.S. (Pp. 223+vii. 16s.) London: Cassell. 1961.

Funktionelle Neurologische Diagnostik. By Dr. med. Harri Joschko. Band I. Periphere Nerven. (Pp. 171+xv; illustrated. No price.) Veb Gustav Fischer Verlag: Jena. 1961.

Sex and the Love Life. By William J. Fielding. Foreword by Harry Benjamin, M.D. (Pp. 298+xx. 3s. 6d.) New York: Permabooks. 1961.

Relief of Symptoms. Second edition. By Walter Modell, M.D., F.A.C.P. (Pp. 374. 86s.) London: Henry Kimpton. St. Louis: The C.V. Mosby Company. 1961.

Die Rohsäfte-Kur. By Eugen Heun (Dr.med., Dr. phil.). (Pp. 286.) Second, enlarged edition. Stuttgart: Hippokrates Verlag. 1961.

Pathologische Reaktionen der Personlichkeit Neurosen und Psychogene Psychosen. By Professor Dr. med. Nikola Schipkowensky. 2 Teil. (Pp. 445.) Wien: Wilhelm Maudrich Verlag. 1961.

Hearing Aids. Issued by the National Institute for the Deaf. N.I.D. Booklet NS/01. (Pp. 16. 6d.) London: National Institute for the Deaf. 1961.

The Nature of Sleep. Ciba Foundation General Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Maeve O'Connor, B.A. (Pp. 416+xii; illustrated. 50s.) London: J. and A. Churchill Ltd. 1961.

Oxytocin. Proceedings of an International Symposium held in Montevideo, 1959. Edited by R. Caldeyro-Barcia and H. Heller. (Pp. 443+xxiv; illustrated. £5.) London: Pergamon Press Ltd. 1961.

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VACCINATION AGAINST INFLUENZA

Advice on the use of influenza vaccine has been prepared by a subcommittee of the Joint Committee on Poliomyelitis Vaccine (which is under the chairmanship of Lord Cohen of Birkenhead), and a note based on the subcommittee's report was sent last week by the Chief Medical Officer of the Ministry of Health to the chairmen of local medical committees and to medical officers of health.

The vaccine which the subcommittee recommends for use "in certain specified circumstances" is a combined influenza A and B vaccine. The most important component of this is the A strain. There has been no major antigenic change since 1957, when the Asian strain appeared, but there were signs of minor changes in antigenicity in strains isolated earlier this year. Strain A/England/1961 is slightly different from A/Singapore/1957. It remains to be seen whether there is any further antigenic shift this year, but in the meantime a vaccine containing the Asian strain should give a reasonable measure of protection—and might do even better if both the England and Singapore variants were included.

The general view in the United States still seems to favour polyvalent vaccines containing virus strains responsible for influenza epidemics during the past 30 years or so. There is no evidence that these vaccines are in any way superior to a monovalent vaccine containing the A2 strain. The trial of vaccine in 1957 seemed to prove this.[1] The inevitable dilution of the essential antigen in a polyvalent vaccine cannot be beneficial.

The subcommittee recommends a single subcutaneous dose of saline vaccine containing the Asian virus antigen. This could be qualified by saying that if influenza should have a late onset in Britain this winter and that three to four months had elapsed since the giving of the vaccine and the appearance of an epidemic, then it might be advisable to give a second dose to those most in need of protection.

[1] Fourth Progress Report of the Medical Research Council by its Committee on Influenza and Other Respiratory Virus Vaccines, *Brit. med. J.*, 1958, 1, 415.

[2] *Brit. med. J.*, 1960, 2, 1145, and 1959, 2, 748.

Immunity to influenza depends on the presence of antibody and also on non-specific factors. The latter are difficult to assess, and consequently it is impracticable to give exact guidance about the duration of immunity. Individuals without antibody and exposed to influenza do not necessarily contract it. On the other hand, antibody resulting from immunization lasts only a few months. After vaccination antibody levels usually decline to about one-half of the initial value in a year, and so, depending on the circumstances, reinforcing doses may have to be given.

The subcommittee has not recommended routine immunization of all sections of the population and "was of the opinion that the vaccine given in this way could not be expected to make a significant contribution to the control of outbreaks of the disease." In previous years we have suggested[2] that patients for whom influenza constitutes a special hazard may be thought by their family doctor to be particularly suitable for influenza vaccine, and the subcommittee suggests five categories of patients who might benefit from annual inoculation with a saline vaccine during the early part of the autumn: those with chronic pulmonary disease, those with chronic heart disease, those with chronic renal disease, those with diabetes (and possibly other less common endocrine disorders such as Addison's disease), and expectant mothers whose pregnancy will extend into the winter months, particularly those who suffer from chronic lung or heart disease. This list, the subcommittee emphasizes, is not intended to be inclusive of all possible disorders calling for vaccination against influenza. With the threat of a large epidemic immunization would be advisable for all those engaged on essential services.

The maximum degree of protection given by influenza vaccines in the most favourable circumstances has been 75%. Provided vaccines contain the correct strains and are given at the right time they should protect from 40% to 60% of the recipients.

But what is the form-ridden general practitioner in the N.H.S. to make of what appears to be a conflict of opinion between the Joint Committee on Poliomyelitis Vaccine, which as we have shown takes a reasonably favourable view of influenza vaccine, and the Standing Joint Committee on the Classification of Proprietary Remedies, which earlier this year classified in category O appropriate proprietary vaccines of the type approved by the Poliomyelitis Committee—that is, a preparation not "standard" which in the Committee's (Proprietary Remedies) view has not been proved of therapeutic value? In the *Supplement* this week Dr. John Little describes this as "a piece of apparent nonsense." He might have left out the word apparent.

SCHIZOPHRENIC SYNDROME IN CHILDHOOD

The multitude of terms used by psychiatrists to describe serious disturbances in the behaviour and adjustment of children reflects a general uncertainty about their nature and aetiological basis. "Childhood schizophrenia," "infantile autism," "childhood dementia," "symbiotic psychosis syndrome," "atypical development," and "schizophrenic syndrome," or "psychosis in childhood," as well as the disorders associated with the names of Kanner, Bender, Mahler, Weygandt, Heller, and De Sanctis, refer to disorders that are similar to or overlap with one another. This abundance of clinical labels has tended to confuse and complicate rather than advance the process of establishing a rational classification. The reasons for uncertainty are not hard to seek and they lead to the heart of the problems of differential diagnosis. In the well-differentiated personality of the adult the effects exerted by psychotic illness, cerebral damage, and extreme emotional stress may be identified fairly reliably. The relative prominence of intellectual decline, emotional disturbance, the degree of social maladjustment, and the incidence of certain consistent clinical symptoms and signs (such as those characteristic, for example, of the schizophrenic or affective psychoses) vary in the different categories of illness.

The situation is less clear with the unfolding cerebral or mental equipment of the child. Severe emotional disturbance is prone to produce marked intellectual retardation or derangement, while the earliest manifestations of cerebral disease may be those of a behaviour disturbance indistinguishable from the way a child will respond to vicissitude or deprivation. Moreover the relative frequency of brain damage and mental defect on the one hand and psychotic disturbance on the other is the reverse of that which obtains in adult life. Muteness or incapacity for communication increases the difficulties of ascertaining precisely what functions are deranged. For all these reasons the effects of psychosis, brain injury or disease, severe emotional stress, and disabilities such as epilepsy and deafness are far more apt than in the mature individual to blend imperceptibly with one another.

This situation has led many workers[1,2] to question whether "childhood schizophrenia" or "autism" has any claims to being an entity at all. This reflects some misunderstanding of what an entity in psychiatry, or in medicine for that matter, implies, and the purpose and value of defining it. Schizophrenia of adult life is no more of an entity in an aetiological sense than Bright's disease or Parkinsonism. It has become increasingly clear in recent years that psychoses occurring in the course of chronic epilepsy[3] or those sometimes associated with dextroamphetamine intoxication[4] or brain injury,[5] may be almost indistinguishable in their clinical features from schizophrenia unconnected with brain damage. Again, in the schizophrenias of the aged it has recently been shown[6] that lifelong anomalies of personality, social isolation, bereavement, deafness, genetic factors, and, in a minority of cases, cerebral degeneration probably all contribute to causation. The difficulties of differential diagnosis of adult schizophrenia are therefore in many respects similar to those of schizophrenia in childhood: the difference is a matter of degree rather than kind.

Yet the relationship between childhood and adult schizophrenia is far from clear. Although a similar hereditary basis has been claimed for the two disorders by some workers,[7] in the experience of most a family history of schizophrenia is uncommon. It is also rare in the extreme to see schizophrenic illness in adult life which is a recurrence of a childhood psychosis, and there is no agreement whether the final picture of childhood schizophrenia, when traced into the adult years, remains one of retardation and withdrawal[8] or is complicated by the delusions and hallucinations of adult schizophrenia.[9] Though there are certain similarities in the clinical picture between the adult and childhood forms, there is much to be said for the use of a neutral term, such as "childhood psychosis," which permits independent specification of the underlying aetiological factors.[10]

The report[11] in last week's *Journal* of a group of workers under the chairmanship of Dr. Mildred Creak who have been examining case material during the past eighteen months to clarify these issues makes a valuable contribution to the definition of the clinical picture of psychosis in childhood. They emphasize nine features, of which only the first was invariably present: the last was also considered by some to be pathognomonic. These features are: gross impairment of the capacity for emotional relationships, unawareness of personal identity to a degree inappropriate for age, an unaccountable preoccupation with particular objects, sustained and obsessional resistance to any changes in the environment, abnormal perceptual experiences, excessive and seemingly illogical anxiety, failure or regression in speech development, distortion of motility, and, finally, serious intellectual retardation with surviving islets of normal or exceptional abilities. To these may be added evidence of archaic thinking and persistent negativism.

Certain differences from the picture of adult schizophrenia are at once apparent. More relevant here is the relatively greater proportion of cases in

childhood in which cerebral damage contributes to causation. Hence it is even more necessary than in adult cases always to assess the contribution of a wide range of possible aetiological factors (genetic, cerebral, emotional, social, sensory defects, and epilepsy). Yet the evidence suggests that, although overlap is greater, here, too, the organic, psychotic, and neurotic territories are distinguishable. Differentiation between them is important for prognosis and treatment. Notwithstanding the multiplicity of organic syndromes that have been described, the cases in which there is no clue to the underlying aetiology are probably in a majority. An important step in differentiating such a broad functional group from other cases is taken when the alternative possibilities of cerebral damage, encephalitis, deafness or blindness, severe neurotic disturbance, and epilepsy are even considered.

A clearly established period of normal development preceding the oddities of behaviour strongly suggests psychosis rather than mental deficiency, although there are cases of the former in which emotional unresponsiveness and withdrawal are evident from the beginning. Careful neurological investigation and observation of the patient's behaviour with other children and at play will generally yield useful information. In the child with organic damage the deficiencies of cognitive function are more uniform, and, in contrast to the psychotic child, the patient is clearly attempting to compensate for deficiencies in order to master his environment. The psychotic child will, however, often fail to apply abilities which are evidently intact to deal with reality. There is a suggestion that social classes I and II (at the upper end of the scale) are over-represented among the parents of non-organic cases.[12] The presence in the parents of marked coldness, eccentricity, or gross rigidity and obsessionality (particularly stressed by L. Kanner[13] in connexion with infantile autism) tends to be associated with functional illness although many parents prove to be emotionally normal.[14] Extreme anxiety, obsessive ruminations, preoccupations with death, depersonalization, and unreality feelings, in the absence of other features, are probably never schizophrenic, even when they appear to engulf the child's personality, but are analogous with certain severe adult neuroses that may on occasion likewise temporarily assume psychotic features.[15] The E.E.G. is of considerable help, particularly in the separation of cases with the specific features found in epilepsy and inclusion-body encephalitis, and will often provide some aid in the diagnosis of deafness in a very young child. In the hyperkinetic syndrome, first described by F. Kramer and H. Pollnow,[16] the child may be cold, cruel, ruthless, destructive, and difficult to contact emotionally, but the condition is distinct from schizophrenia: about 50 to 60% have epileptic fits or electroencephalographic evidence of focal lesions,[17] and many of the remainder probably have some more subtle cerebral anomaly. The disturbance often becomes attenuated with advancing age and the prognosis is better than in autistic children.

So far as treatment is concerned, in deafness, epilepsy, and certain other cerebral conditions specific remedies may mitigate the organic disease and the behaviour disturbance with it. In the presence of mild cerebral lesions the brain disease merely contributes to, rather than causes, the psychosis, and the prognosis is not necessarily hopeless. In the schizophrenic-like psychosis associated in adults with epilepsy[3] or slight cerebral damage[18] the psychosis may take a favourable course, probably because such individuals are less predisposed genetically than subjects in whom an intact cerebrum provides no protection against becoming schizophrenic. A similar state of affairs may well hold in the case of children, although there have been far too few follow-up studies for any firm opinion to be possible. In the general run of cases the non-appearance or regression of speech is an unfavourable feature.

Physical treatments such as E.C.T. and insulin coma have proved worthless, but phenothiazine derivatives can be useful in controlling restlessness, excitement, and extreme agitation. Whatever the form of treatment, it can work only at several steps removed from the processes that sustain the illness. In the opinion of most psychiatrists these children, with rare exceptions, grow up with personalities that are damaged to varying degrees, and even the 20% recovery rate claimed by R. S. Lourie and his colleagues[19] is considered too sanguine. The value of intensive psychotherapy is clearly limited, but improvement and recovery do occur, possibly in groups awaiting definition, and long-term management should include some attempt to penetrate the barrier that emotionally isolates the child,[12] and to

[1] Mahler, M. S., Furer, M., and Settlage, C. F., *American Handbook of Psychiatry*, 1959, New York, Vol. 1, p. 816.
[2] Stroh, G., *J. Child Psychol.*, 1960, **1**, 3, 238.
[3] Slater, E., Paper delivered at Maudsley Symposium on Epilepsy and Mental Disorder, 1959, London Institute of Psychiatry. To be published.
[4] Connell, P. H., *Amphetamine Psychosis*. 1958, London.
[5] Maller, O., in Congress Report, 2nd International Congress for Psychiatry, 1957, Zurich, Vol. 1, p. 102.
[6] Kay, D. W. K., and Roth, M., *J. ment. Sci.*, 1961, **107**, 649.
[7] Kallman, F. J., and Roth, B., *Amer. J. Psychiat.*, 1956, **112**, 599.
[8] Kanner, L., and Eisenberg, L., *Psychopathology of Childhood*, 1955, ed. by Hoch and Zubin, New York.
[9] Bender, L., *Amer. J. Psychiat.*, 1954, **110**, 855.
[10] Creak, M., Congress Report, 2nd International Congress for Psychiatry, 1957, Zurich, Vol. 1, p. 102.
[11] *Brit. med. J.*, 1961, **2**, 889.
[12] Anthony, J., *Brit. J. med. Psychol.*, 1958, **31**, 211.
[13] Kanner, L., *Z. Kinderpsychiat.*, 1958, **25**, 108.
[14] Creak, M., and Ini, S. J., *J. Child Psychol.*, 1960, **1**, 2, 156.
[15] Roth, M., *J. Neurol. Psychiat.*, 1960, **1**, 293.
[16] Kramer, F., and Pollnow, H., in *Mschr. Psychiat. Neurol.*, 1932, **82**, 1.
[17] Ingram, T. T. S., *J. ment. Sci.*, 1956, **102**, 550.
[18] Krauss, S., Congress Report, 2nd International Congress for Psychiatry, 1957, Zurich, Vol. 2, p. 100.
[19] Lourie, R. S., Pacella, B. L., and Piotrowski, Z. A., *Amer. J. Psychiat.*, 1943, **99**, 542.

help him re-establish his contact with, and differentiation from, the objective world.

To advance inquiries in this field a firmly based classification is urgently needed. The problem need not be insuperable. Diagnostic features such as those defined in the recent report of Dr. Mildred Creak's working party are very valuable, but what is needed next is a generally agreed procedure for their application in the selection of cases. The clinical, psychological, neurological, and electroencephalographical investigation of a carefully selected sample of children should help to determine the relative frequency of the different items and the weighting they ought to receive when diagnosis is being decided. It should also provide more precise knowledge of the different organic and functional syndromes and the degree of overlap between them. With this information available research into causation will start from a better position.

DOSAGE FOR THE NEWBORN

It is a matter of common knowledge that within a short time of the introduction of a new drug, particularly a potent chemotherapeutic agent, reports appear of toxic and sometimes fatal side-effects which, from the initial animal experiments and preliminary clinical trials, come as a surprise. Such reports concerning newborn or premature infants may be less surprising when one considers that the original experiments are likely to have been done on adult animals, not on newborn.

In a recent review of the toxicity of drugs to newborn babies W. L. Nyhan[1] pleads for further studies on the peculiarities of paediatric—and particularly neonatal—pharmacology, and his report certainly substantiates his plea. He suggests that new drugs should be screened on newborn animals before release for giving to the newborn infant and that the drug firms should be required to establish, before marketing, the presence or absence of differential toxicity in the newborn. This would entail extensive clinical trials in the nurseries and wards of maternity hospitals before routine dose schedules were accepted. There are so many possible factors which determine the neonatal response to drugs that simple extrapolation from size (whether by weight or surface area) will not suffice to assess a safe and effective dosage. No formula has yet been described which can be applied to neonatal life, nor is a nomographic method much more satisfactory. These can provide only approximate information, and it may not be accurate enough for any given infant. So far, personal experience has proved the most valuable guide in determining dosage for newborn infants; as Goodman and Gilman[2] say: "The dose for infants should be learned as such and not calculated by formulae."

In addition to differing from the older child or adult in size and surface area the newborn baby, and even more the premature, show remarkable differences in metabolic processes. These materially alter the rate and efficiency of absorption, detoxification, and excretion of drugs, and the dosage needed will vary accordingly. Nyhan cites such factors as inefficient glucuronidation, limited capacity for acetylation, and delayed development of microsomal oxidate systems in the liver. The immaturity of kidney function in premature infants is also important in that it may permit drugs to reach much higher levels in the blood than they would attain in later infancy.

Several reports have drawn particular attention to the possible toxic effects of chloramphenicol, sulphafurazole, and vitamin K, all of which have been, and still are, extensively prescribed in nurseries for the newborn and in units for premature babies. Serious risks attend the use of these preparations routinely and they have all three caused a number of deaths. Chloramphenicol is undoubtedly a valuable, potent, and toxic drug; most doctors respect it and limit its use to certain specific infections in whose treatment its values may be expected to outweigh the possible risks. But, as has been emphasized recently in these columns,[3] the clinical picture of its toxic effects in newborn and premature infants is different. Initial vomiting and reluctance to feed are followed by the development of an ashen-grey cyanosis, hypothermia, and hypotonia; death from peripheral vascular collapse may occur within a few hours. The causative factor seems to be related to the deficiency of glucuronyl transferase, which normally conjugates chloramphenicol. It is therefore of the utmost importance that the dose of chloramphenicol in the newborn should be carefully limited; it should not exceed 25 mg. per lb. body weight (55 mg. per kg.) per day for full-term infants or 12.5 mg. per lb. body weight (27 mg. per kg.) per day for premature infants. Sulphafurazole has special dangers for premature infants, whose powers of sulphonamide acetylation are limited, for it may compete with bilirubin for binding sites on serum albumin and so displace protein-bound bilirubin, thereby leading to hyperbilirubinaemia and kernicterus.[4] W. A. Silverman and colleagues[5] described an "epidemic" of kernicterus in a nursery for premature babies where

[1] Nyhan, W. L., *J. Pediat.*, 1961, **59**, 1.
[2] Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 1956, 2nd Edition, Macmillan Co., New York.
[3] *Brit. med. J.*, 1961, **1**, 1019.
[4] Odell, G. B., *J. Pediat.*, 1959, **55**, 268.
[5] Silverman, W. A., Anderson, D. H., Blanc, W. A., and Crozier, D. N., *Pediatrics*, 1956, **18**, 614.
[6] Allison, A. C., *Lancet*, 1955, **1**, 669
[7] Hofnagel, D., *New Engl. J. Med.*, 1961, **264**, 168.

penicillin and sulphafurazole were given together as a routine prophylactic and the sulphafurazole was incriminated as being responsible. The haemolytic effect of the 1,4-naphthoquinones is well known. Their special effect in premature infants was originally reported by A. C. Allison,[6] and subsequently many papers have recorded cases of kernicterus after large doses of vitamin K. These can all be avoided in future by using vitamin K_1 in a dose not exceeding 1 mg.

Clearly these drugs should not be used as routine prophylactics, nor should chloramphenicol be the first choice for treating established infection in the newborn unless blood levels can be regularly determined. As alternatives, streptomycin 125 mg. (62.5 mg. for a premature infant) at 12-hourly intervals for a maximum of four doses (three for premature babies) is a safe and effective drug both prophylactically and therapeutically; so are the tetracyclines in doses of 25 mg. per lb. body weight (55 mg. per kg.) per day, all by intramuscular injection. Combinations of streptomycin and penicillin are potentially dangerous, for though the mixture may contain the desired amount of penicillin it may have too much streptomycin, which could cause toxic effects on the central nervous system, particularly coma. A number of such cases have occurred in America. Even atropine eye-drops have been found to produce toxic effects.[7] There are doubtless other drugs which are a particular hazard to the newborn, and the special vulnerability of these young patients needs to be borne in mind.

SUPPORT FOR RESEARCH ON TROPICAL ANAEMIAS

Probably the majority of the world's population is anaemic as judged by commonly accepted normal values, though the extent to which different peoples are affected is not easy to assess. Anaemia is certainly a major cause of morbidity, and A. W. Woodruff[1] has emphasized that it is a public-health problem of world-wide dimensions. Thus in a recent study in Vellore, South India, M. Jadhav and S. J. Baker[2] found 14% of children admitted to the department of paediatrics to have a haemoglobin value less than 7.5 g. per 100 ml. of blood. At another extremity of the Indian sub-continent H. Foy and A. Kondi[3] found 15% of the population with 8 g. or less of haemoglobin per 100 ml. of blood. Of tropical Africa H. C. Trowell[4] has stated, "Some degree of anaemia is present in the majority of the men, women, and children of many areas." Woodruff and F. D. Schofield[5] found 10% of Gambians to have less than 8 g. of haemoglobin per 100 ml. of blood. There are many reports indicating a similar state of affairs in the tropical Americas, Pacific islands, and Far East.

The cause of the majority of these anaemias is iron deficiency, usually a consequence of parasitism and especially of hookworm infection. Megaloblastic anaemias are common by European standards, and there are anaemias associated with such malnutritional states as scurvy, kwashiorkor, and protein deprivation. The hereditary haemoglobinopathies form an important group of which sickle-cell anaemia is the principal member. In many types of anaemia in the tropics, however, the cause is obscure, as has been emphasized by M. Payet and his colleagues,[6] who, working in Dakar, reported that no cause could be found for 20% of the anaemias there. They suggest that nutritional, genetic, and sociological factors affect the characteristics of the pathological responses of Africans, and that though they acquire a dearly won equilibrium with their environment this is always precariously balanced.

The complex aetiologies of the tropical anaemias add to the difficulties of their control. Even when the cause is reasonably certain, as, for example, in much iron-deficiency anaemia, control on a public-health scale is a daunting proposition. G. J. Stott[7] showed that a supplement of as little as 6 mg. of iron per day would prevent most anaemia in Mauritius, but even so the fortification of foodstuffs or even the distribution of pills presents great technical difficulties. In most parts of the tropics it has been found that iron-deficiency anaemia becomes relatively uncommon only when the living conditions of the population have improved to the stage of wearing shoes and using satisfactory latrines. Only then are hookworm infections and the iron losses they cause eliminated and the dietary iron rendered adequate.

Clearly, then, there is a pressing need for co-operative research on a broad basis and in several countries, and satisfaction will be widespread that the Wellcome Trust has decided to give, among other donations (see p. 969), £100,000 toward the expenses of research on anaemia of the tropics. Nearly half this sum will be used to establish a Wellcome Laboratory of Tropical Haematology in Professor J. V. Dacie's department at the Postgraduate Medical School, Hammersmith. This laboratory, with its wide Commonwealth associations, will serve as the home base, and the work there will be co-ordinated with that of Dr. Foy in Kenya, Dr. Baker at the Christian Medical College, Vellore, and R.A.M.C. officers in Singapore, all of whom are studying anaemia associated with the malabsorption syndrome. Support for the Wellcome Sprue Unit is to continue for a further five years, and a special grant has been made for the purchase of *x*-ray equipment needed there for a new method of investigation. Much more than money will be needed to elucidate the complex causes of the tropical anaemias, but all those concerned with raising the standards of health in underdeveloped countries will be encouraged by the Wellcome Foundation's generous grants for essential research.

[1] Woodruff, A. W., with Fairley, N. H., and Walters, J. H., *Recent Advances in Tropical Medicine*, 1961, London.
[2] Jadhav, M., and Baker, S. J., *Indian J. Child Hlth*, 1961, **10**, 235.
[3] Foy, H., and Kondi, A., *J. trop. Med. Hyg.*, 1957, **60**, 105.
[4] Trowell, H. C., *Non-Infective Disease in Africa*, 1961, London.
[5] Woodruff, A. W., and Schofield, F. D., *Trans. roy. Soc. trop. Med. Hyg.*, 1957, **51**, 217.
[6] Payet, M., Linhard, J., Pene, P., and Armengaud, M., *Med. Afr. noire*, 1957, **4**, 355.
[7] Stott, G. J., *Trans. roy. Med. Hyg.*, 1961, **55**, 20.

CORTICOSTEROID EXCRETION IN OBESITY

Fat children and adults on an average excrete more 17-ketogenic or 17-hydroxysteroids than do those of normal weight[1-5]; the values may exceed the upper limits of normal for age and sex. The output of 17-ketosteroids has been reported variably in obese children as normal[1] or slightly raised[2] and in obese women as diminished[3] or increased.[5] In a large series of obese women J. Poisnick and V. DiRaimondo[3] found normal levels in plasma but increased urinary output of 17-hydroxysteroids. In 16 obese men P. Szenas and C. J. Pattee[4] reported low levels in plasma and increased urinary output of these steroids. Injected cortisol hemisuccinate disappeared more rapidly from plasma and the ratio of conjugated to free 17-hydroxy-corticoids in plasma was higher in the fat men than in those of normal weight. These workers concluded that both production and metabolic removal of cortisol were probably increased in obesity. Radioisotope studies will be needed to confirm whether secretion is increased. The changes reported in plasma could be due at least in part to dilution in a greater volume and absorption of steroid by fat depots.

At this stage one can only speculate on the clinical significance of these alterations in steroid metabolism. It is most unlikely that the adrenal cortex is a primary factor in the causation of simple obesity, for when fat children are put on a restricted diet their urinary 17-ketogenic steroids fall readily to normal levels[2 5]; and a positive correlation exists between corticosteroid excretion and body mass in healthy children and adults.[6-8] If secretion of cortisol is indeed increased, this could, as H. Cohen suggests,[2] be due to a direct effect of overnutrition on pituitary or adrenocortical function.

In simple obesity there are clinically few, if any, signs of increased adrenocortical activity. The stigmata of Cushing's syndrome are so numerous, varied, and individually non-specific that it is not surprising that one or several of them are often found in obese patients. Recently B. Simkin[5] has analysed the incidence of these signs in 62 fat women and has related them to the urinary 17-ketogenic steroids. Only in four patients with coloured striae were these steroids above the normal range; when other signs, such as diabetes, hirsutism, and hypertension, were present, the output of steroids did not exceed the mean level for the group as a whole.

DEATH OF A WEEKLY JOURNAL

In its 123rd year *The Medical Press* ceased publication with its issue dated September 27, 1961. The news of this unhappy event was not preceded by the customary rumours that prepare readers and staff for such an unpleasant surprise. The only information given in the last issue of this notable periodical was the following laconic message appearing under the heading "Vale": "We greatly regret to have to inform our readers that owing to the pressure of constantly increasing costs *The Medical Press* is to cease publication with this issue after 122 years of existence as an independent weekly medical journal." Increasing costs have laid low national newspapers and now what the publishers correctly describe as "an independent weekly medical journal"—a fact which all who have the interests of medical journalism at heart must deplore.

The Medical Press was until of late years better known as *The Medical Press and Circular*, and when it celebrated its centenary in 1939 the first paragraph of the editorial commenting on this ended thus: "... our thoughts at the moment are fixed not upon the past but upon the present and the future, for we feel that a great responsibility rests upon us to maintain without faltering the high standards and ideals of those responsible for our birth."[1] The future unfortunately has come to an end. In the past, the journal was founded in Dublin in 1839 as the *Dublin Medical Press* by Dr. Arthur Jacob and Dr. Henry Maunsell, the former professor of anatomy and physiology and the latter professor of midwifery in the school of the Royal College of Surgeons in Ireland. Arthur Jacob, who had been an apprentice of William Colles, practised as an ophthalmic surgeon. The new journal was published in the same year in which Richard Carmichael founded the Irish Medical Association. As the history of *The Medical Press and Circular*, written in the centenary number by Professor Robert T. Rowlette, shows, Jacob was the driving force behind the new journal, the predominant aim of which was medico-political. He remained editor until 1860, when he was succeeded by his son, Dr. Archibald Jacob, as editor until 1865. In 1866 the *Dublin Medical Press* amalgamated with the *Medical Circular*, founded in 1852 by Dr. James Yearsley, an aural surgeon who practised in London, the first medical man, according to R. Scott Stevenson,[2] to practise solely in diseases of the ear and throat in London. Yearsley founded the Metropolitan Ear Institution, which eventually became the Metropolitan Ear, Nose, and Throat Hospital. Yearsley was also one of the originators and first editors of the *Medical Directory*.

The amalgamation of the two journals under the title *The Medical Press and Circular* led to a shift of emphasis from Ireland to England, and its change in this direction was probably accelerated by the fact that the publisher was Mr. A. A. Tindall, whose name is so familiar to the medical profession in the description of that well-known firm Baillière, Tindall and Cox, the publishers who have had to yield to financial *force majeure* by bringing to an end a medical periodical one of whose objects at its inception was "To rouse the slumbering energies of the Irish practitioner," and which subsequently carried this missionary spirit across the Irish Channel to the southernmost part of the British Isles.

1 Gray, C. H., Lunnon, J. B., Pond, M. H., and Simpson, S. L., *J. clin. Endocr.*, 1956, **16**, 473.
2 Cohen, H., *Brit. med. J.*, 1958, **1**, 686.
3 Poisnick, J., and DiRaimondo, V., *J. clin. Endocr.*, 1956, **16**, 957.
4 Szenas, P., and Pattee, C. J., ibid., 1959, **19**, 344.
5 Simkin, B., *New Engl. J. Med.*, 1961, **264**, 974.
6 Norval, M. A., and King, N., *Biometrics*, 1950, **6**, 395.
7 Talbot, N. B., *et al.*, *J. clin. Endocr.*, 1951, **11**, 1224.
8 Borth, R., Linder, A., and Riondel, A., *Acta endocr. (Kbh.)*, 1957, **25**, 33.

1 *Med. Press*, January 25, 1939, p. 65.
2 Ibid., p. 115.

NATIONALITIES AND TURNOVER OF HOSPITAL JUNIOR MEDICAL STAFF

SURVEY BY THE SHEFFIELD REGIONAL HOSPITAL BOARD

The Sheffield Regional Hospital Board had a census on January 24, 1961, to ascertain the nationalities of the junior medical staff (registrars downwards) in hospitals in its region. For the sake of convenience of reference the nationalities are divided into two groups: (A) English, Scottish, Welsh, and Irish (Northern Ireland and Eire); and (B) all others.

Table I shows that there were approximately 58% group B doctors in posts in the region on the date in question as compared with 51% which was reported to the Platt Committee on Medical Staffing Structure in the Hospital Service. There is no evidence to suggest that the position is now stable and that the dilution of group A doctors will cease.

TABLE I.—*General Analysis of Doctors in Post by Nationality*

	Registrar	J.H.M.O.	S.H.O. and H.O.	Total
No. of posts ..	171	45	243	459
Posts vacant ..	9	10	19	38
Group A doctors	63	19	96	178
,, B ,,	99	16	128	243

Table II indicates that although the average of group A doctors in the region was 42%, some hospitals were completely or almost completely staffed by doctors from overseas.

TABLE II.—*Percentage of Group A Doctors to Total Number of Posts on Establishment*

Percentage of Group A	Hospitals with Staff Numbering				Total All Hospitals
	1–5	6–10	11–20	21+	
Nil	20	6	—	—	26
10–20	—	5	—	1	6
21–30	2	5	2	—	9
31–40	2	1	1	—	4
41–50	3	1	—	—	4
51–60	—	3	—	1	4
61–70	4	—	1	3	8
71–80	2	2	—	—	4
81–90	—	—	—	—	—
100	9	—	—	—	9
	42	23	4	5	74

The language, feeding, accommodation, and other problems which arise from a large number of different nationalities working and living together must be known to all concerned. The language problem not only creates difficulties within the hospital; discourse with general practitioners and patients' relatives can also produce complications. It will be seen, for example, that one hospital with a medical staff in the 11–20 category (in actual fact 18) had a junior staff composed of 10 different nationalities (Table III).

TABLE III.—*Number of Different Nationalities in Hospitals with a Medical Staff of Five or Over (Group A is Represented as One Nationality)*

No. of Different Nationalities	Hospitals with Staff of 5–10	Hospitals with Staff of 11–20	Hospitals with Staff of 21 or Over
1	1	—	—
2	5	—	—
3	6	—	—
4	6	—	1
5	5	2	1
6	—	1	1
7	—	—	1
8	—	—	1
9	—	—	—
10	—	1	—
	23	4	5

Nationalities by Specialty

The survey indicated that certain specialties seemed less attractive than others to the indigenous doctors, and the following are of particular interest:

1. *Chest Diseases and Infectious Diseases.*—Out of 16 posts, only 3 were held by group A doctors; all the remainder were filled by group B doctors, largely by Indians (10).

2. *E.N.T.*—Only one group A incumbent in seven appointments; five posts were held by Indians and one was vacant.

3. *Orthopaedics and Casualty.*—Out of 49 posts, only 8 were filled by group A doctors. In addition, six posts were linked general surgery/casualty, and only one of these was filled by a group A doctor.

4. *Thoracic Surgery.*—There are seven appointments; one was vacant and the other six were filled by group B doctors.

5. *General.*—General medical and obstetrical and gynaecological posts had about 50% of group A doctors and general surgery rather less with 26% of group A doctors.

Four-year Survey

In addition to the one-day census referred to above the whole registrar position (130 posts) was surveyed over the period January 1, 1957, to December 31, 1960. (N.B.—Only the grade of registrar was surveyed, because the Board possessed the records of this grade; the other grades are Hospital Management Committee appointments.) This survey revealed the following:

Vacancies.—This analysis was undertaken by specialty, but nothing of particular significance could be demonstrated from the figures except that some posts were extremely difficult to fill; for example, during the four years in question, out of 130 posts 10 were vacant for over 12 months, 12 for over six months, and 12 for periods of four to six months.

Turnover of Registrars.—There are certain difficulties in analysing turnover for a short period of four years, as even if registrars complete the normal two-year tenure it is possible for three registrars to occupy one registrar post for some time in the four-year period. However, the tenure of the 214 registrars who actually started and ended their appointments during the four-year period is shown in Table IV.

TABLE IV

	6 Months and Under	6–12 Months	12–18 Months	18–24 Months	Over 24 Months	Total
Group A ..	12	20	12	13	5	62
,, B ..	38	70	24	17	3	152
	50	90	36	30	8	214

When it is borne in mind that a registrar appointment is normally one of two years, it is disappointing to note that 65% actually terminate in 12 months and under, and that some 23% serve for under six months.

The figures show that in regard to remaining in post group B is less stable than group A, although even in group A the turnover would appear to be more rapid than it should be. In group A 51% remain in post less than 12 months, and in group B 71%.

Nationalities of Applicants for Registrar Posts

The nationalities of applicants for 705 registrar posts in the Sheffield Region advertised during the period July 1, 1959, to December 31, 1960, have been analysed (Table V).

TABLE V

	Group A	Group B	Total	Three Largest Groups in Group B
(*a*) Details of actual applications received	131	921	1,052	Indians (669). Pakistanis (75). Australians (44)
(*b*) Nationality of short-listed applicants	106	639	745	Indians (451). Pakistanis (55). Australians (40)
(*c*) Nationality of short-listed applicants who failed to attend for interview	27	300	327	Indians (207). Pakistanis (29). Australians (22)
(*d*) Nationality of applicants who actually attended for interview (i.e., *b*–*c*)	79	339	418	Indians (244). Pakistanis (26) Australians (18)
(*e*) Nationality of successful applicants	50	138	188	Indians (87). Australians (15). Two others (5)

The following points are of particular interest: (1) Out of the 705 posts advertised 134 had no applicants, or where there were applicants they either withdrew their applications before the interview or were not considered suitable for appointment by the Hospital Management Committee. (2) Apart from (1) above, 132 of the advertisements produced no group A applicants at all. (3) It will be seen that although 1,052 applications were received for these posts the effective applicants were reduced to 418 after those not suitable and those who failed to attend for interview although invited had been deleted. (4) The large number of candidates who failed to attend for interview although invited (31%). (5) Of the 188 appointments made, 27% were group A and 73% group B.

General Comments

The reader can draw his own conclusions from the above statistics, and the main purpose in publishing them is to make them available to anyone who is undertaking research associated with medical staffing.

These statistics go further than those available to the Platt Committee (Report of the Joint Working Party on the Medical Staffing Structure in the Hospital Service), as nationalities of applicants and turnover of registrars have been analysed.

The survey is based on research undertaken by Mr. E. M. Sharman, D.P.A., A.H.A., Assistant Secretary (Medical Division).

"In Dar es Salaam, in the busiest of our four dispensary out-patient clinics, up to 1,600 patients a day are seen by one medical officer and five or six medical assistants; calculation reveals that the time available is under two minutes each. What is the right answer to this problem? Should we deliberately practise a lower standard of medicine in order to spread it further? If we do we lay ourselves open to attack by the more sophisticated who realize they are not getting all they might. This attack may take the pointed form of a legal action for negligence. I do not know if our legal brethren would accept the defence that it is better to treat ten patients indifferently than one patient well. If, however, we insist on maintaining the highest possible standards it is evident that the time and money available will be used up on the first few patients, while the remainder will get no attention at all. I do not know the answer. Whatever is done is open to criticism. I am quite sure it is wrong to have two standards of practice, a higher one for the more sophisticated and a lower for those unlikely to object. A possible guide may be for us to aim at the highest standards and to justify the limited output by using it to train. Those trained will then be able to help the remainder." (Dr. A. C. E. COLE, presidential address on opening the Annual Conference of the Association of Physicians of East Africa, 1960. *East African Medical Journal*, June, 1961.)

EUROPEAN ASSOCIATION AGAINST POLIOMYELITIS

[FROM A SPECIAL CORRESPONDENT]

The Seventh Conference met at Oxford from September 17 to 20, under the presidency of Professor HENRY LASSEN (Denmark). The first day was spent discussing poliomyelitis vaccination, 14 delegates giving details of vaccination status and morbidity figures.

Vaccination Campaigns

In the Federal Republic of Germany two injections of 0.5 ml. and a booster dose a year were given to approximately 600.000 people in each of the three years 1958–60, from a population of 55 million. The rate of paralytic poliomyelitis was 2.5 per 100.000 in 1958, 3.24 in 1959, and 5.72 in 1960. Sweden, with a population of 7.5 million, had a better although not a satisfactory vaccination rate. Pre-schoolchildren, then schoolchildren, and then persons under 50 received three suitably spaced doses of 1 ml.: 70% of those aged 9 months to 6 years, 95% of those 7–19, and 20% of those over 20 years were immunized with inactivated vaccine and a few with live attenuated vaccine. The rate of paralytic poliomyelitis per 100.000 (hereafter p.p.) was 2.1 in 1958, 0.34 in 1959, and 0.13 in 1960. Coincident with this was a great reduction of poliomyelitis virus recovered from samples of stools in the general population. Their figures illustrated that parents, though anxious to have their children inoculated, were themselves needle-shy. Some delegates pointed out that these figures could be improved by the general practitioner giving injections. The difficulty of comparing results is enormous: in Denmark the technique is two intradermal injections, a total of 0.3 ml., the interval being one month, and a third dose about a year later. The acceptance rate was 98% for those aged 14 years and under, 80–90% for those aged 15–19, and 70–80% for all below 40. The p.p. rate was 1.5 in 1958, 0.2 in 1959, and 0.1 in 1960 compared with 15 in 1951–5, the pre-vaccination years.

There is no doubt that there is a higher acceptance rate for dead or live attenuated vaccine after epidemics such as Hungary had in 1957 when 2.334 cases occurred, and again in 1959 with 1.830 cases, incidences of about four and three times the average for 1952–9. In Hungary, with a population of about 10 million, in 1958 6.5 million doses of Salk vaccine were given, in 1959 0.9 million doses of Salk vaccine were given and 2.6 million doses of Sabin vaccine, and in 1960 5.1 million doses of Sabin vaccine were given. The p.p. rates in the three years 1958–60 were 1.7, 18.3, and 0.38. In 1960 the acceptance rate for children aged 0–14 was 94%. In Finland, where the acceptance rate for Salk vaccine was 20–25% in children, 0–15% in adults, and less than 10% in the total population, the p.p. rates for the years 1958–60 were 2.2, 6.8, and 6.1. Nevertheless for the first six months of 1961 it was 0.6. In many instances trivalent vaccine (type I, II, and III) was given.

Live Attenuated Vaccine

The countries using live vaccine extensively are the U.S.S.R., Czechoslovakia, and Poland. In Poland, with a population of 29.5 million, the p.p. rates for 1958–60 were 21.1, 3.8, and 0.9. In 1958 10 million doses of Salk vaccine, in 1959 7.5 million doses of type I and 7.1 million of type III live vaccine, and in 1960 3 million doses of Salk vaccine were used. The 7 millions immunized with live Koprowski vaccine were 80.9% of children aged 6 months to 15 years, and there was the greatest reduction of cases in this group, i.e., from 2.275 to 236, whereas in those over 14 years the figures fell from 162 to 39. They later propose to give type II and a booster type I, and to extend vaccination to those under 25. The figures for Czechoslovakia are quoted in some detail because their representative replied to cross-

examination generously and lucidly. The population is 13.5 million, the p.p. rates for 1958–60 were 1.81, 1.51, and 0.46. In 1958 approximately 3 million doses of Salk vaccine and 143,377 doses of Sabin type I vaccine were given: in 1959 309,507 doses of Salk vaccine and 114,510 of Sabin type II and 127,290 type III, and in 1960 100,000 doses of Salk vaccine to pregnant women and 3.5 million of Sabin type I and 3.5 million of type III. The acceptance rates for Sabin vaccine was approximately 90%, about 50% higher than for Salk vaccine. This massive attack on poliomyelitis—chiefly in children—resulted in an exceptionally high standard of immunity, "a decrease of the raised morbidity to zero figures was recorded in the period of the usual peak," and the disappearance of polio virus at the peak of the usual season. No confirmed cases of poliomyelitis have occurred from June, 1960, to August, 1961. They propose to immunize children born later. During this campaign neither tonsillectomy nor inoculations against diphtheria, tetanus, etc., were interrupted.

In the U.S.S.R. 13.5 million people were given live Sabin vaccine in 1959, 77.5 million in 1960, and 70 million in 1961. Provinces rather than age groups were selected for mass immunization. Safety appears undoubted. The general programme was type I, followed by trivalent vaccine (type I, II, and III). The immunological response corresponded to that obtained with the best Salk vaccine. Feeding types I, III, II at intervals gave the best results, but single trivalent feeding or a dose type I followed by types I, II, III gave good results also. Virus excretion in those without antibodies was approximately twice as long as in those with antibodies. Virus transmission to contacts, especially in families, seemed helpful. Failure to acquire immunity might be due to interference by non-polio viruses, especially E.C.H.O. viruses. In those regions now immunized with Sabin vaccine the incidence in 1958–60 was not dramatically lowered, although there was a fourfold reduction of paralysis in those receiving Salk vaccine. The Sabin vaccine controlled epidemics and eliminated seasonal peaks. Salk vaccine was useful in preventing paralysis, but did not alter the seasonal peak.

In England and Wales the p.p. rates for 1955 to 1960 have been 8.6, 2.3, 7.2, 3.2, 1.6, and 0.6. In 1961 provisional figures suggest a rise and that type III has caused more paralysis than type I. Vaccination with modified Salk vaccine continues, 13.6 million doses having been given in 1958, 17.3 in 1959, and 7.6 million in 1960. Sabin-type vaccine is on trial, and is being held in reserve for epidemics, probably by heterotypic blanketing (e.g., type II Sabin vaccine to combat a type I or III epidemic).

Conference's Conclusions

In the discussion, a plea was made and accepted for expressing titres of antibodies against standard sera; for the family to be used as the minimum unit; for "not changing bicycles when going downhill"; for giving Sabin after Salk; and for recognizing the higher acceptance rate with oral vaccine, the stubbornness of adults, and rarity of Bell's palsy being caused by poliomyelitis.

Professor G. S. WILSON (London), summarizing the reports and discussion, said both vaccines appeared safe: The live vaccine showed no signs of resuming virulence, and the Salk vaccine if prepared correctly was also safe. Both produced a good antigenic response. The live vaccine conferred intestinal immunity, and the Salk vaccine did not interfere with wild virus in the gut. The duration of immunity was unknown with live vaccine, nor did we know how often Salk or Sabin vaccine had to be repeated. Sabin's vaccine appeared to confer better herd immunity, was easy to administer, was cheaper, more acceptable. Salk's method had a possible advantage in allowing wild strains more often to reinforce immunity by invasion of the gut later. The meeting supported the following "agreed" statement:

> The Conference examined very carefully the comparative merits of the inactivated (Salk) and the living attenuated (Sabin) vaccines in protecting against poliomyelitis. Considerable difference of opinion among the delegates was revealed, and it became clear that no generally accepted policy for Europe could be agreed upon until further information was available, especially on the degree and duration of immunity conferred by the two vaccines.
>
> Attention was drawn to the extensive use of the live vaccine in the U.S.S.R., Czechoslovakia, and other parts of Eastern Europe: and the great convenience of the vaccine, which is given by the mouth instead of by injection, was noted.
>
> It was thought that, for the present, the choice of vaccine should be left to the individual countries to decide in the light of their particular problems and administrative capabilities. Countries contemplating the introduction of the live vaccine might well consider using it, in the first place, in combination with the inactivated vaccine.

This statement implies lack of knowledge. Questions still to be answered relate to the ideal combination, the best age, the treatment of the pregnant woman, and the necessity to reinforce national (Salk- or Sabin-type) immunity.

Miscellaneous Papers

Drs. M. DU PAN, J. RAST, M. PACCAUD, and S. GUBLER (Switzerland) reported observations which showed that pregnant women immunized by two doses of Salk vaccine transmitted antibodies to the neonate. These interfered with the child's production of antibodies if he were given live vaccine soon after birth. However, at 6 months, when partial immunity was still present, live vaccine (each type being given separately) provided good immunity. Mr. W. J. W. SHARRARD (Sheffield) reported that serial sections and reconstruction of the motor-cell columns of the spinal cords of poliomyelitis patients, the distribution of whose muscular paralysis before death was known, showed that the motor cells were destroyed in these columns. Some muscles like tibialis anterior were supplied by a small column: other muscles by large columns which were seldom extensively destroyed.

Poliomyelitis still has its clinical problems. Dr. S. THIEFFRY *et al.* (Paris) had studied 4,173 cases of enterovirus infection of the C.N.S. in children. Clinical and virological studies of poliomyelitis were in close agreement, but there were some extraordinary forms. Eight had ataxia, which, though excessively severe initially, was sometimes followed by almost complete recovery in a fortnight. Six had extrapyramidal lesions followed by Parkinsonism in two. One had hypotonia and mutism. Of seven who had C.N.S. involvement due to five E.C.H.O. and two Coxsackie viruses, four had paralysis or cerebellar disturbances. Dr. N. R. GRIST (Glasgow) reported that poliomyelitis as a cause of paralysis had been displaced by other enteroviruses in Scotland, the chief being Frater virus and Coxsackie A7. The latter virus had been associated with seven paralytic illnesses, one of which was fatal. Dr. H. PETTE (Hamburg) had also found evidence that Coxsackie A7 caused paralysis and this could be reproduced in the monkey. He reminded the meeting that Chumakov, Voroshilova *et al.* had in 1952 isolated this virus type from the faeces of paralysed patients in an epidemic of 260 and indeed regarded it as type IV poliomyelitis virus.

In 1959 the Committee of Ministers of the Council of Europe instituted a yearly programme of co-ordinated medical fellowships on subjects of common European interest. One of the subjects chosen was camping hygiene and sanitation, and the team responsible for the investigations have now published a booklet, *Camping Hygiene*, which gives details of what the members found in various countries in Europe. The report is divided into three parts: "Camping Legislation and Organization," "Health and Hygiene in Camping," and "Facilities and Entertainment." General conclusions and recommendations are also given. As the introduction to the booklet observes: "The stimulating effect of climatic variations and the day and night cycle experienced in the open are beneficial to the thermo-regulating system and to physical and mental health alike." (H.M.S.O. No price quoted.)

FIRST INTERNATIONAL CONGRESS OF EXFOLIATIVE CYTOLOGY

[FROM A SPECIAL CORRESPONDENT]

The First International Congress of Exfoliative Cytology was held in Vienna from August 31 to September 2. A major topic at the meeting was pre-invasive cervical carcinoma.

The Commonwealth provided an outstanding contribution to the control of cancer in the shape of the first complete report from British Columbia. D. A. BOYES, H. K. FIDLER, and D. R. LOCK, of Vancouver, recorded that 1,100 practitioners in that province were now taking exfoliative cytological tests at regular intervals. The target for these tests was pre-invasive cervical carcinoma, a curable disease. Unless unequivocal evidence of a diminution in *invasive* cancer followed the widespread removal of *pre-invasive* carcinoma of the cervix in their huge sample of the community, they proposed to shut down their cytological screening programme. There was no question of this happening, for they could show a fall in invasive carcinoma of 25% over the period 1951–61, and it seemed certain that this figure would rise steadily as more women submitted to yearly tests. In the Province of British Columbia, at present, one out of every four women considered to be at risk was submitted to regular exfoliative cytological tests. The importance of this study as a challenge to all who are anxious to prevent cervical cancer is quite clear: carcinoma of the cervix must now be accepted as a preventable disease, at least in women who are willing to submit regularly to cytological tests.

Carcinoma-in-situ

The Conference proceeded to study the nature of carcinoma-in-situ (or pre-invasive carcinoma) of the cervix with special reference to whether or not it might disappear either spontaneously or with simple therapy. Careful clinical workers such as E. BURGHARDT, of Graz, and his colleagues, using cytology and colposcopy as clinical aids, were prepared to leave a known cervical lesion in certain patients eager to have a child. But the need for caution was emphasized, for there was always the possibility that when conization of the cervix was finally carried out the clinician might be dismayed to find not simply carcinoma-in-situ but also a small area of invasive carcinoma.

L. G. KOSS reported that in the Memorial Hospital, New York, his group had made a prospective study of 70 cases with carcinoma-in-situ and epithelial dysplasias (not carcinoma-in-situ); 25% had progressed towards malignancy, 50% disappeared, and 25% remained stationary. The degree of epithelial abnormality and the future behaviour of the lesion could not be correlated with certainty—for example, lesions which appeared microscopically innocuous might be followed by invasive carcinoma, while "aggressive-looking" lesions might disappear. Moreover, the degree of surface differentiation, the relative orderliness of the epithelium, and the size of the carcinoma cells were found to be without meaning in establishing a prognosis. Trichomonal infection and intervening pregnancies appeared to have no direct effect on the behaviour of the lesion. Koss and his colleagues emphasized that they took a serious view of borderline cervical atypia, whether or not it was labelled carcinoma-in-situ or epithelial dysplasia. The fate of epithelial dysplasia in the gynaecological or pregnant patient was also the subject of a study from New Orleans by C. M. DOUGHERTY and his colleagues. Although certain that healing (perhaps temporary) was common, they nevertheless regarded it as mandatory to perform a cone biopsy on any cervix presenting marked epithelial atypism.

Pregnancy and the Cervix

The effect of pregnancy on the cervix was compared to traffic lights by H. C. MCLAREN and M. E. ATTWOOD, of Birmingham, England. One per cent. of a series of 5,000 consecutive pregnant women had yielded positive or "suspect" smears. A "strongly positive" report represented a red light: carcinoma-in-situ. A report that the cervix was producing epithelial cells with dyskaryotic nuclei was compared to a "caution," an amber light, and, although not necessarily a pointer to immediate conization for diagnosis, it was most certainly a warning. Cone biopsy, prompted by a cytological report of dyskaryosis and performed as soon as possible after delivery, might produce histological evidence of not only dysplasia but carcinoma-in-situ. After delivery, however, the patient might become normal both clinically and cytologically. This was not an indication to discharge the patient. Her progress should be followed for an indefinite period, since after two or more years she might develop a positive smear and histological evidence of carcinoma-in-situ. The experience of T. A. SLATE and his colleagues in San Diego was in line with the observations from Birmingham. They especially underlined the worth-whileness of screening the pregnant woman. They regarded dyskaryosis as a very early sign of pathological change, a pointer to future carcinoma-in-situ and therefore a pointer to lifelong follow-up.

Was it possible that carcinoma-in-situ could disappear temporarily after pregnancy? It could perhaps be shed in pregnancy and involution, or, if unifocal, disappear as a result of healing after biopsy, but all speakers agreed that once diagnosed histologically carcinoma-in-situ must be subjected to conization. No other form of biopsy would both exclude the presence of any area of carcinoma and also offer an excellent prospect of cure of the carcinoma-in-situ without hysterectomy.

Committee on Definitions

The value of some agreed histological standards in reporting experience from all parts of the world is obvious but very difficult to achieve. The Committee considered that the definition used by Kottmeier at the 1954 British Congress of Obstetricians and Gynaecologists for invasive carcinoma, "tissue independently and actively growing in the stroma," should replace the term micro-carcinoma. If the carcinoma on histological study was of small size this should be stated. Carcinoma-in-situ should show practically no epithelial differentiation—that is, to qualify for the term carcinoma-in-situ all epithelial layers should be involved. Occasional exceptions with coexistent areas of superficial differentiation should be reported in detail and not otherwise included in statistical reports under the heading "carcinoma-in-situ." Finally, disturbances in differentiation (*Unruhigkeit*) in epithelium should be reported objectively with no attempt to imply that its future behaviour was being forecast. Rather than atypia or anaplasia the term agreed to was "dysplasia" (marked, moderate, or slight).

The Committee have written a booklet on definitions which will be welcomed by all gynaecological pathologists. A parallel study and recommendations in exfoliative cytology is also to be published by the Cytology Terminology Committee under the chairmanship of G. L. Wied; this will be equally welcome when it becomes available later in the year.

Technical Aids

D. S. ROME (United States), using acridine fluorescent dyes, had attempted to sort the few positive cells in an exfoliative smear from the large number of negative ones, by means of mechanical aids. Although at present her results were inconclusive, it was apparent that many people in the discussion which followed were anxious to find a reliable, time-saving mechanical aid in screening. Further studies with dyes and radioactive isotopes were proposed, for success in this field would be of immense value in large-scale screening programmes. J. Z. CRESPO (United States)

showed that much information could be obtained about cell activity in the endometrium by histochemical methods. He also showed some very clear pictures of enzyme distributions in cells during different stages of the menstrual cycle. One would have liked more technical information about the preparation of his material.

A. I. SPRIGGS and R. F. ALEXANDER (Great Britain) described an elegant method for detecting malignant cells in the blood using the relative specific gravities of the red cell, the white cell, and the malignant cell. Applying strict criteria to the description of the cells isolated by their improved technique, they found a low incidence of circulating cells in known cases of carcinoma. This differed markedly from earlier workers, who had reported a high correlation between carcinoma and cells circulating. The recovery of cells liberated by a tumour and detected by this method was too low to serve as a diagnostic method.

Evidence from the Mouse

W. M. CHRISTOPHERSON (United States) showed the development of atypical epithelial lesions in the mouse following exposure of the cervix to the carcinogenic action of methylcholanthrene. Repeated exposure to this agent produced correlated cytological and histological pictures of atypical lesions progressing to a picture of carcinoma-in-situ, observed through all four Papanicolaou cytological stages and finally to frank invasive carcinoma. This experimental evidence gave much support to the clinical evidence of the progressive nature of atypical lesions of the cervix.

The Conference was wise to narrow its study to certain themes and to limit severely the number of speakers, allowing adequate time for discussion of groups of papers. *Acta Cytologica* will publish all the papers in full.

METHOTREXATE IN THE TREATMENT OF CANCER

[FROM A SPECIAL CORRESPONDENT]

On September 18 Lederle Laboratories invited about 70 people to a one-day symposium on the subject of methotrexate in the treatment of cancer. This meeting was held at the Royal Society of Medicine, and Professor FRANZ BERGEL, F.R.S., was the chairman.

Professor E. BOYLAND, Chester Beatty Research Institute, London, gave the first paper. He spoke of the history of folic acid and the antifolic acid drugs. Folic acid and its derivatives were required for introducing single carbon atoms into other molecules—for example, into positions 2 and 8 of the purine structure. Sarcoma 180 was dependent for its growth on folic acid, but it was the clinical work of Farber and others at Boston, using folic acid antagonists in the therapy of acute leukaemia in children, which had really started the interest in methotrexate as an anti-tumour agent.

Absorption, Clearance, and Toxicity

Dr. MARION FREEMAN-NARROD, Department of Pharmacology, Oxford, discussed the absorption and plasma clearance of methotrexate in the human subject. She had studied the plasma concentration of methotrexate in the children given this drug for acute leukaemia at the Children's Hospital, Boston. Of the 18 patients investigated all but four showed the highest plasma concentration of methotrexate one hour after oral administration, and all the drug had been excreted three hours later. The remaining four patients absorbed the drug more slowly, and still had a high concentration after three hours. These four patients showed early signs of drug toxicity such as ulceration of the mouth. When 14 of the patients were investigated after they had been on the drug continuously for six weeks, it was found that eight of nine patients who had previously absorbed the drug rapidly now did so slowly. The four patients whose absorption curve was slow originally were unable to take the drug for six weeks because of toxic side-effects. If the drug were given intravenously the plasma of the patients was clear of methotrexate very rapidly irrespective of the type of absorption curve.

In the discussion following these two papers Dr. R. D. SULLIVAN, Boston, suggested that his work with intra-arterial methotrexate showed that toxicity to this drug was not related to its concentration in the blood but to the time the tissues were exposed to it. Dr. W. JACOBSON, Cambridge, suggested that all the toxic effects of methotrexate could be explained by inhibition of mitoses in rapidly dividing cells.

Clinical Applications

Mr. W. P. GREENING, Royal Marsden Hospital, London, then reported on the use of methotrexate in 37 cases of advanced breast carcinoma. Oophorectomy had been performed in 20, and these cases were considered by some to be of no value in assessing the effect of the drug. However, Mr. Greening showed pictures of patients who had not had oophorectomy performed but who had experienced regression of skin deposits, and he considered that six of seventeen of these patients were improved by the drug. He was using a dose of approximately 5 mg. per day continuously.

Dr. K. BAGSHAWE, Charing Cross Hospital, London, reviewed the work of Hertz and others on the treatment of chorionic tumours with methotrexate, and then described 13 cases of chorion epithelioma he himself had treated with methotrexate and 6-mercaptopurine. Four patients had died within five days of starting therapy. Six of the remaining nine cases showed complete regression of tumours and return of gonadotrophin levels to normal. He gave these drugs together in 4- to 5-day courses. The doses were 20 to 25 mg. per day of methotrexate and 300 to 600 mg. per day of 6-mercaptopurine. The morning ended with a talk by Dr. A. C. MUIR, the Royal Infirmary, Bradford, who gave his experience of the oral use of methotrexate for early carcinoma of the uterus, cervix, and vulva. Nine women had each received a total of 125 mg. of the drug in five days. Assessment was made on histological changes at the end of six weeks. No changes were seen, and there were two deaths, one probably due to infectious hepatitis, but one certainly due to drug toxicity. Three cases of ovarian carcinoma were not helped by this regime.

In discussion several other people spoke of remissions in chorion epithelioma using Dr. Bagshawe's regime, and some mentioned the efficacy of methotrexate alone.

Intra-arterial Infusion

The afternoon session was devoted to discussing the intra-arterial infusion of methotrexate in advanced malignant disease. Dr. R. D. SULLIVAN, Lahey Clinic, Boston, presented his findings in approximately 70 cases. In 51 cases the tumours were confined to the head and face, and there were 11 cases of brain tumour. It was important to maintain a fairly low level of methotrexate in the blood, but to keep the drug flowing into the tumour over long periods of time. He gave as little as 5 mg., which he took 12 hours to infuse through the carotid artery, and repeated this daily for four to seven days. The course was repeated when signs of toxicity had abated, and further courses were administered for as long as seven weeks. A dose of 5 mg. per day given in the above manner over five days was considered equivalent in its toxic side-effects to 25 mg. per day given intra-arterially every day in one injection. Of the 51 cases of tumours of the face so treated Dr. Sullivan felt he could evaluate results in only 38; nine tumours had regressed. Some failures were certainly due to the fact that the major blood supply of the tumours was derived from arteries other than those infused with methotrexate. Complications were

caused by misplaced catheters, leakage from the catheter, local infection, and bleeding at the site of insertion of the catheter.

Mr. G. WESTBURY, Westminster Hospital, London, presented results of methotrexate infusion into 39 patients. Thirty-one of these patients had had previous irradiation, and although these patients received 50 mg. per day for two to four weeks there were only three cases in which complete regression occurred. Six patients did not receive intramuscular folinic acid; in two of these patients regressions occurred, but two showed severe falls of leucocyte count and there was one death due to toxicity. Mr. Westbury felt that previously irradiated cases were less likely to show regression and that the use of folinic acid intramuscularly might reduce the local effectiveness of methotrexate.

Mr. H. J. ESPINER, the Royal Infirmary, Bristol, presented 18 cases of intra-arterial methotrexate infusion through the superficial temporal artery. Ten patients had received previous irradiation. A few regressions were recorded.

Intrathecal Administration

Dr. B. M. LAURANCE, Derbyshire Children's Hospital, described two children with acute leukaemia who developed cerebral and cranial deposits at a time when the peripheral blood and bone marrow were practically normal. In each case 10 mg. methotrexate was put into the cerebrospinal fluid three times over five days. The cerebral symptoms and signs subsided and the skull deposits regressed. One patient survived another 8 months and the other 5 months. Both died in haematological relapse, and there were no side-effects from the intrathecal use of the drug.

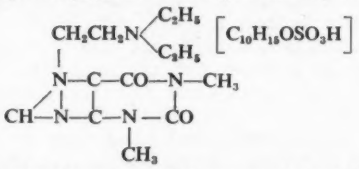
The proceedings were concluded by Professor BERGEL. It is hoped that a book will be published shortly presenting the papers and discussions in full.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

"Millophylline" (Dales Pharmaceuticals).

Chemistry.—This is a camphor sulphonate of diethylaminoethyl theophylline. It is represented by the formula:



It is soluble in water and gives a neutral solution.

Pharmacology.—Millophylline is a loose combination of three drugs—theophylline, diethylaminoethanol, and camphor. The actions of theophylline are well known, for it is a frequently prescribed cardiac and respiratory stimulant in the form of aminophylline (theophylline ethylenediamine). It increases the amplitude and rate of cardiac contraction, increases the rate and depth of respiration when this is depressed, and dilates the smooth muscle of the bronchi. In addition it is an effective diuretic. The manufacturers claim that in millophylline these actions of theophylline are modified in two respects; the heart rate is not increased and the diuretic response is reduced. Diethylaminoethanol, a metabolite of procaine, stimulates cardiac contraction and can restart the heart after the cardiac arrest produced by acetylcholine. It also has an antifibrillatory effect similar to that of quinidine. Camphor salts have been known for many years to have some slight effect as cardiac and respiratory stimulants, but they are seldom used for this purpose. In short the pharmacological activity of millophylline as a cardiac and respiratory stimulant would appear to differ only in minor respects from that of the parent substance theophylline. In addition to these main actions millophylline is said to stimulate contraction of the uterus and it is also claimed that it enhances the activity of skeletal muscle.

Therapy.—Millophylline is available in tablets of 0.1 g. and in ampoules containing 0.7 g. in 5 ml. for intramuscular injection. A solution for intravenous injection can be made by diluting 2.5 ml. of the intramuscular solution in 7.5 ml. of sterile water. The indications for its use are those conditions in which theophylline or aminophylline are commonly used. These are bronchial or cardiac asthma (paroxysmal cardiac dyspnoea), Cheyne-Stokes respiration, respiratory depression (e.g., after anaesthesia, sedation, or in the newborn), cardiac failure, and occasionally in cardiac ischaemia with severe angina or myocardial infarction. The therapeutic value of theophylline compounds when given intravenously in some of these conditions, notably acute left ventricular failure and Cheyne-Stokes respiration, is well recognized, but there is considerable doubt about the therapeutic efficacy of any of the currently available oral preparations of theophylline and its derivatives. There is as yet insufficient clinical evidence to indicate that in these conditions millophylline is superior to older and well-established theophylline compounds, and it is difficult to believe that the minor modifications in pharmacological activity which are claimed as the result of forming such a complex substance can confer any considerable therapeutic advantage. The manufacturers state that millophylline is of value in uterine inertia, but good evidence for such a claim would be needed before it can be generally accepted. The drug has also been used by mountaineers and athletes to enhance muscular activity and counteract fatigue.

Side-effects.—It is claimed that tablets of millophylline do not give rise to gastric irritation and that intramuscular injections are painless. In high dosage the drug may give rise to insomnia from stimulation of the central nervous system.

N.H.S. Basic Price.—100 tabs. 0.1 g., 14s.; 6 amps. 5 ml., 5s. 8d.

Selenium Sulphide

"Lenium" (Bayer Products).
"Selsun" (Abbott Laboratories).

Therapy.—The treatment of dandruff by local application of products containing selenium sulphide was introduced several years ago and has on the whole proved most useful. In the form of an emulsion or suspension selenium sulphide is applied to the scalp and left on for only 10 or so minutes before being thoroughly washed out. Applications are repeated at intervals of one to three weeks according to the individual response to treatment. In most cases it is desirable to start treatment at fortnightly intervals and to make treatments more or less frequent than this according to progress. In many cases it is found that this treatment will completely remove dandruff and irritation, leaving the scalp normal. If treatment is stopped, however, it is usual to see a gradual relapse so that after six or eight weeks the scalp has returned to its previous condition.

Side-effects.—A few cases of dermatitis, presumably due to allergic sensitivity, have been reported from the use of this remedy. Selenium sulphide is a toxic substance and the makers' instructions draw attention to the need for careful cleansing of the scalp and hands after treatment has been carried out. Some workers have suggested that selenium sulphide may interfere with the growth of hair and help to cause baldness, but the evidence for this does not appear at all conclusive. In practice these side-effects or drawbacks are seldom material, and for many patients applications of selenium sulphide provide a satisfactory solution to an annoying and sometimes distressing complaint.

N.H.S. Basic Price.—Lenium, 4 oz., 8s. 6d.; selsun suspension, 4 fl. oz., 6s. 10d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Intramuscular Injections

Sir,—In your annotation (September 16, p. 758) on the optimum site for intramuscular injection the use of the anterolateral compartment of the thigh is briefly dismissed in favour of a particular site on the buttock, on the ground that a haematoma may arise in the vastus externus muscle. I have never seen such a haematoma and believe it must be a very rare complication.

May I urge that the outer side of the thigh is the safest and best place for intramuscular injections and quote my old friend and mentor, Professor Grey Turner ?[1 2] Following injections into the buttock he was able to collect six cases of foot-drop with varying degrees of anaesthesia, some cases of painful and severe sciatic neuritis, and at least two cases of severe secondary haemorrhage from the superior gluteal artery complicating abscesses. My experience supports what he wrote: The vastus externus is a very large muscle; it is protected by the fascia lata and is not traversed by any important vessels or nerves. A point on the middle of the outer side of the thigh should be used, and here the needle may be thrust in for an inch (2.5 cm.) or more. No harm can be done even if the needle strikes the femur; should it do so, it is withdrawn a little before the injection is made.—I am, etc.,

Surgical Unit,
Royal Infirmary, Cardiff. Lambert Rogers.

References

[1] Grey Turner, G., *Lancet*, 1920, **2**, 819.
[2] —— *Brit. med. J.*, 1944, **2**, 56.

Sir,—The late Professor C. E. M. Joad would have said: "It all depends what you mean by 'the buttock'" (September 16, p. 758). And this is the difficulty in a nutshell. What medical men do not always appreciate is the nurse's problem when it comes to anatomy. The nurse sees a very different buttock from the doctor. She has not spent the most impressionable three months of her life—her first three months out of school—wearily dissecting, for several hours every day, every last fibre of the buttock. Because the doctor has done just that, he sees the buttock as in Fig. 1, and knows that the upper and outer quadrant (left), or the area he can reach with his fingers if his thumb is on the anterior superior iliac spine (right), does not contain the sciatic nerve.

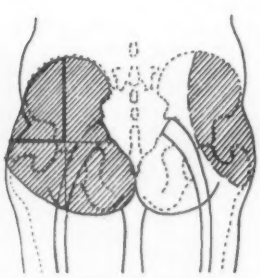


Fig. 1.—The doctor's view of the buttock.

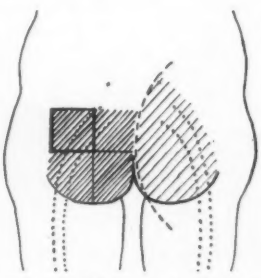


Fig. 2.—The nurse's view of the buttock.

But the nurse sees the buttock as the area shaded on the left of Fig. 2. The buttock, to her, is the "cheek" of the buttock. She dutifully divides this area into four quadrants, as has so often been drummed into her, quite unaware that now the upper and outer quadrant hardly contains anything else but the sciatic nerve. Occasionally she tries the manœuvre of putting her thumb on the anterior superior iliac spine and injecting into the area her fingers can cover. But, with the patient lying on his side or his face, it is so very easy to use the tip of the great trochanter instead, with the result that the whole length of the sciatic nerve in the buttock now lies within the field of fire (Fig. 2, right). Only the thickness of the gluteal fat and the gluteus maximus protects the nerve in 90% of intramuscular injections into the buttock.

There is no fool-proof rule of thumb for avoiding accidents. The only answer is a knowledge of anatomy and more accurate training. Sister tutors can do this, but it is the ward sister who has the most telling opportunity when she shows the junior probationer how to give an intramuscular injection into the buttock for the first time in real life. It is to our ward sisters that we must look to raise the standard in future generations of nurses.—I am, etc.,

Canterbury, Kent. F. G. St. Clair Strange.

Hypnotic Suggestion

Sir,—The two articles on hypnotism published in your issue for September 16 require some comment, especially as at the moment considerable research is being undertaken using hypnotism both as a therapeutic and experimental tool.

With regard first to the congenital ichthyosiform erythrodermia (p. 741). One would need to hear from Dr. C. A. S. Wink, not only about what appears to be objective changes in the skin, but also detailed information concerning the local treatment of the skin following hypnotic suggestion. In two cases of my own, of the same condition, objective improvement seemed to be occurring, but in fact the improvement was due entirely to increased exfoliation of the skin due to vigorous mechanical abrasion. The increased scrubbing of the skin occurred in those areas in which I had suggested improvement and was due in one case to the desire of the patient to conform with my suggestions that the hard black skin would come off. The patient subsequently suppressed the information about the scrubbing (probably unconsciously) and it was only by accident that it was discovered. In the second case, the mother of the patient, probably through the intense desire to produce something to please me, and so not abandon what was her last hope, scrubbed the areas very much more vigorously following my suggestions. Both cases in fact when hospitalized went back to their original condition.

Whilst I am not for a moment suggesting that this has happened in Dr. Wink's case, it is important for him to make clear that he has excluded this possibility. It has become evident to recent workers in this field that the patient has an intense desire to please or placate the hypnotist and will sometimes claim to be well, when there is no objective evidence of this, or even, as in the two ichthyotic cases I have mentioned, will produce an apparent improvement by unconscious cheating.

Following my original case of ichthyosis treated in 1952, I have since attempted to treat eight other similar cases without success. Why one case responded and the

others did not still remains a mystery. One case, however, of epidermolysis bullosa did respond.

Referring now to the paper by Dr. Stephen Black and Mr. E. R. Wigan (p. 736), in which they report the apparent production of deafness in several subjects by hypnotic suggestion. The subjects were conditioned to respond with an increased pulse rate to a note which had been previously reinforced with an electric shock. The shock of course causes pain and the increase of pulse rate is a typical anxiety response to this. Following conditioning, the note alone produces the anxiety response.

Now it is common knowledge that direct suggestion in the hypnotic state will alleviate anxiety of an acute and sometimes even of a chronic nature. For example, patients with conscious anxiety, say about a stage performance, can have this diminished by direct hypnotic suggestion, or patients with unconscious anxiety—that is, phobias—can be made to overcome them whilst in the hypnotic state. In both the above situations it is simple to demonstrate that the pulse rate is unaltered following the suggestion that the patient will not mind the experience, whereas previously there was a tachycardia, when exposed to the painful experience. Dentists employ this phenomenon frequently in the treatment of acutely anxious patients.

It is no argument to say the patient could not infer that the suggestion made was meant to diminish anxiety simply because this was not specifically stated. Saying, "You will not hear the note," is the same as saying to the conditioned patient, "You will not experience it as painful, and therefore do not need to react as you would normally do to pain," i.e., tachycardia, etc. In fact Dr. Black and Mr. Wigan already point out that patients infer unconsciously different things from the same suggestion.

Dr. Black and Mr. Wigan have demonstrated therefore, I believe, that the anxiety response to an unpleasant stimulus can be abolished by hypnotic suggestion, but not yet that true deafness has been produced. Many workers have demonstrated that the anxiety response (tachycardia, electrogalvanic reflex, etc.) to an unpleasant stimulus can be removed by direct hypnotic suggestion. Dr. Black and Mr. Wigan have really only confirmed this, as it were, once removed, by tacking on the anxiety response to a note. This is not a demonstration that there is actual blockade of the note itself. There is an interesting confirmation of this within the experiment in the spreading of the blockage of the stimulus through different frequencies of the note in some subjects. It is a well-known psychological phenomenon that when one suppresses an anxiety-provoking stimulus one may suppress all sorts of things related to that stimulus as well. For example, a patient with a phobia about horses may easily have also distaste for riding-crops, habits, etc. We know, moreover, that Dr. Black and Mr. Wigan's Welsh subject had considerable anxiety concerning certain traumatic past experiences of noise connected with loss.

It is difficult to see how the paper by Dr. Black and Mr. Wigan may prove to be relevant when attempting to treat conversion hysteria, as they infer, and I would remind them of the example Dr. Stafford Clark recently gave of a conversion hysteria, treated by symptom-removal, who then immediately committed suicide. Whether they have produced deafness, as they believe, or an absence of anxiety, as I believe, this is still no reason for suggesting that hypnotism is a suitable treatment for conversion hysteria, which will always need some form of psychotherapy.—I am, etc.,

King's College Hospital,
London S.E.5. A. A. Mason.

Treatment of Tetanus

Sir,—In areas with little tetanus, medical staffs confronted with a case derive substantial guidance from the publications of centres with greater experience, and the report by Drs. P. M. Smythe and A. B. Bull (September 16, p. 732) constitutes a valuable addition to this literature. One point for discussion is the avoidance by these workers of the need for bronchoscopic removal of obstructing membrane from the tracheobronchial tract. Possibly their high level of humidity permitted this.

Experience in the management of a recent severe case in my practice, which I helped to manage in hospital, shows, however, that for one reason or another such membranes occur in certain cases, that their removal is necessary, and that the early indications for such removal may be overlooked. Clinical features of this patient were as follows.

A 12-year-old girl sustained a leg wound seven days before admission. Her first symptoms were on the day before, and her first spasm on the day of admission. Tracheotomy was done three days, and the bronchoscopic removal of membrane four days, after admission. Other management included having A.T.S., chlorpromazine and phenobarbitone, tube-feeding, high humidity, and repeated cleaning of the tracheotomy tube, and tube-aspiration of the tracheobronchial tract via the tracheotomy tube.

Prior to bronchoscopy there occurred frequent spasms together with moderate accentuation of breath sounds as heard at the opening of the tracheotomy tube. It was at first suspected that the increasing spasms had promoted the noisier breathing and that heavier sedation would be needed (a type of misconception emphasized by Drs. Smythe and Bull), particularly since the tracheotomy tube was unobstructed and the tracheobronchial tree aspirated. The otolaryngologist, however, suspected obstruction, and, after passing a bronchoscope through the incision in the trachea, removed with forceps four circular, dark-coloured membranes from the region of the bifurcation. The membranes were slightly smaller than a threepenny piece and as thick as blotting-paper. Their removal was followed by a transformation of the clinical picture, the breath sounds resuming their almost noiseless character and the spasms stopping completely.

The above sequence of events was repeated almost identically four times during the next seven days, all observers being convinced that the removal of the membranes brought about an immense and dramatic relief of symptoms.—I am, etc.,

Sheffield. Joseph Blake.

Early Maturing and Larger Children

Sir,—Contrary to the opinion you express in your recent leading article (August 19, p. 502) we do not believe that there is anything astonishing about the earlier maturation or increase in size of to-day's children. We agree with those[1] who think this is a very natural consequence of the evolution in infant and child care which has taken place in the past 100 years, the most objective evidence for which is the fall in infant mortality. Heterosis may indeed contribute to secular changes in physical development as you, Sir, suggest, but we feel its contribution has to date been much less important than that of improvement in the environment during childhood. Because of shortage of space we will confine our arguments to the increase in the adult height of males.

Our data were obtained by measuring a random sample of men who were working underground in the coal mines of

the Rhondda Fach at the time of the M.R.C. private census in 1958, together with their entire families. 85% of the parents (fathers and mothers) spent their childhood days in the Rhondda, and for about 80% of both parents at least three of the first 12 years of life—the years which are probably the most susceptible to environmental influence[2]—fell during the economic depression between the wars.

A measure of the effect of this depression on the child health of the community can be obtained from infant mortality data shown in the Figure, where it will be seen that between 1924, when South Wales first felt the effects of the resurgence of the European coal industry, until the outbreak of war in 1939 infant mortality fell less steeply in the Rhondda than it did in England and Wales. There was a fall in 1935 which is coincident with an increase in demand for Welsh coal invoked by the revival of the British steel industry, but this fall was not maintained, and indeed the conditions in the Rhondda were not greatly improved between 1935 and 1939.[3] In contrast, since the second world war the fall in the Rhondda has not differed from that in the country as a whole, although the overall rate remains consistently higher in the former.

These differences are closely matched by the differences in adult height of those whose childhood knew the soup-kitchens of the between-war years, and those who grew up in times of full employment; to the latter we have added the expected adult height of children of skeletal age 7 years or over, predicted from their present height and radiological assessment of their skeletal maturity.[4] Table I shows that the secular increase per decade in height of skeletally mature men born in the mining community of the Rhondda during this century is more than twice as great as the figure you, Sir, give for Western men. In Table II we show that the increase in stature between the two generations of Welshmen is over 2 in. (5 cm.), more than twice the increase you estimate for males. Yet age for age the Welsh children we have studied are smaller than the national average—their group mean falls around the fortieth percentile as estimated by Tanner.[5]

TABLE I.—*Estimated Increase in Male Stature per Decade (inches)*

	Stature		
	n	Mean	s.e. of Mean
Caucasian people* ..		0·39	
Rhondda†	90	0·89	0·27

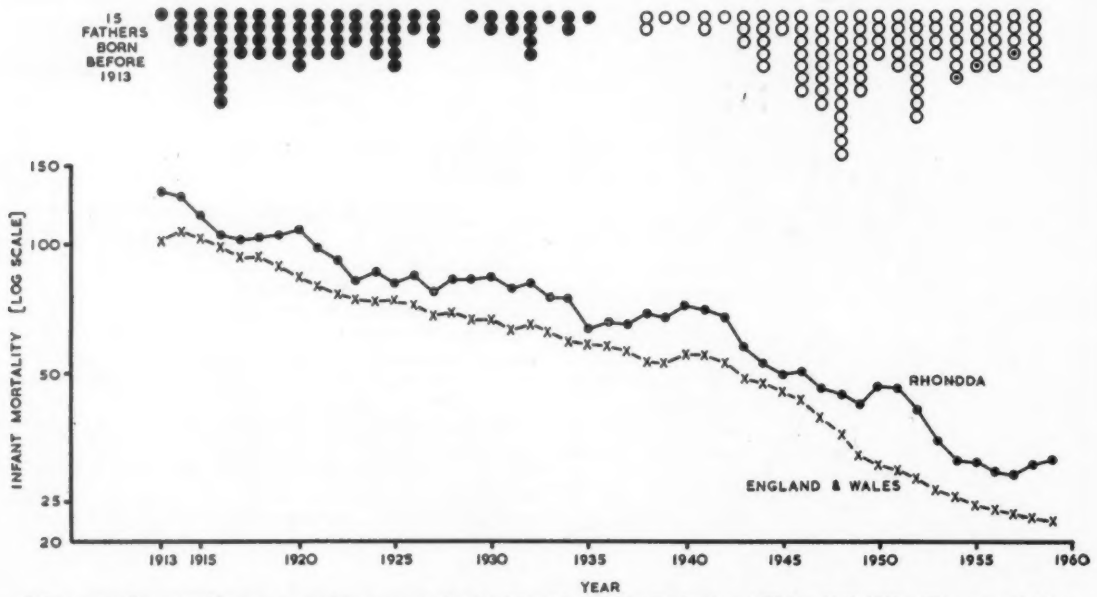
* *Brit. med. J.*, 1961, **2**, 502.
† Calculated from regression of stature upon age at survey of skeletally mature males born 1906–1941.

TABLE II.—*Actual and Predicted Excess in Adult Height of Sons Over Fathers (inches)*

	n	Mean Difference	s.e. of Mean Difference
Mature sons actual difference ..	8	+2·03	0·77
Growing sons predicted difference	70	+2·45	0·39
Mature and growing sons ..	78	+2·40	0·35

In summary, men who grew up in an area where there was profound economic depression, and where the infant mortality was falling less rapidly than the national average, have sired sons who, reared in more prosperous times, are or will be 2½ in. (6.25 cm.) taller than their fathers—over twice the expected between-generation excess. Yet these sons are smaller, age-for-age than the national average, and we suggest that this is associated, in part at least, with the fact that the infant mortality in the Rhondda is still much higher than that of all England and Wales. There is much in the literature to support this view, for there can be little doubt that a deterioration of the environment slows maturation and stunts growth,[6] and it is reasonable to presume that environmental improvement will have the opposite effect. Further evidence comes from the work of Hulse,[7] which as you point out makes a case for the effect of heterosis. He shows that the offspring of exogenous marriages are about 2 cm. taller than those of endogenous marriages of the same defined Swiss stock, whether the children are brought up in Switzerland or in California; he also shows that, both for endogenous and exogenous marriages, children reared in California are 4 cm. taller than those who did not emigrate. In fact the apparent effect of heterosis is additional to that of a change in environment, but the effect of California (presumably environmental) is twice as great.

We believe that as long as infant mortality continues to fall physical development of children will continue



Infant mortality rates (three-year moving averages) for the Rhondda and for England and Wales, 1913–1959. The years of birth of all the males in the sample are shown, and the generations distinguished thus: ● Father, ○ Son, ⊙ Grandson.

to accelerate for *environmental reasons alone*; indeed, this may be an underestimate, for mortality data are a very crude measure of maternal efficiency and acceleration may continue after infant mortality has reached an irreducible minimum. The genetic factors which must be added to this but which we believe are of secondary importance are, as you suggest, heterosis, and possibly the immeasurable one of whether the genotype of the child who now survives because of improved maternal care is the same from the point of view of physique as that of the child who would have been sturdy enough to survive anyway.

We are grateful to Professor A. L. Cochrane for allowing us to use his census population and to Dr. Roy Morley-Davies for unpublished vital statistics from the Rhondda. Our research is supported by the Medical Research Council and Guy's Hospital Medical School.

—We are, etc.,

ROY M. ACHESON.
GILLIAN B. FOWLER.
Guy's Hospital Medical School, London S.E.1.

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Losing Weight

SIR,—Your leading article on losing weight (September 23, p. 814) has maintained your customary high standard of a clear, succinct summing-up of the orthodox opinion to date. You could hardly overemphasize the importance of eradicating from the patients', but also alas many doctors', minds all false information and ideas on slimming remedies. Among those you thought too elementary to mention is the use of hormones and injections of any kind, including diuretics. The kindest thing that can be said of doctors who employ these—and there are still not a few—is that they are displaying their ignorance.

When you suggest that the "unlimited" calorie diet, as advocated by Dr. H. L. Marriott and Professor J. Yudkin, are only effective because they are in fact low-carbohydrate diets and in practice limited-calorie diets, I feel that greater emphasis might be laid on the advantages of this kind of diet from the patient's point of view. He is told, usually to his very great surprise, that he can eat as much as he likes. I have many patients who, whilst still losing weight at a steady pound a week or more (after initial loss), have volunteered the information that they have never eaten so well. I am afraid I cannot agree that the average patient finds it just as easy to convert allowed exchanges of diet in terms of calories as filling in football-pool permutations. I have met doctors who aren't too good at it. Even if you consider that the patient is indeed having fewer calories, the advantage of not having to restrict amounts and of not having to measure or calculate are such as to make the restricted-calorie diet out of date.

It is when you say that sustained weight loss is unaffected by alterations in the proportion of fat, protein, and carbohydrate that I feel you are over-simplifying the issue. I would remind you of the specific dynamic action of protein amounting at a conservative estimate to 25%. This means that if a patient is maintaining his weight on a modest 2,500 calories a day he will have to eat 3,125 calories if he has it all in protein. 3,125 calories in terms of uncooked protein can be represented by the equivalent of 3½ lb. (1.6 kg.) of lean beef steak plus 1 lb. (0.45 kg.) of fresh fillets of haddock. I suggest that this is a real factor in enabling me to tell a patient on an almost pure protein diet that he can eat as much as he likes. I have a number of patients willing to testify that they do, and that in spite of it they are able to maintain a steady loss of 3½ lb. (1.6 kg.) a week after initial fluid loss. I have done it a number of times myself.

Whilst agreeing entirely that each patient should be dealt with by methods best suited to his circumstances and personality, we have surely now reached the stage when we can no longer regard the restricted-calorie diet as the method of choice.—I am, etc.,

London W 9. A. LEWIS.

Herpetic Whitlow

SIR,—We are very glad that you have drawn attention (September 9, p. 696) to this condition, since after our original description of it[1] numerous fresh examples have come to light and there is every indication that it is a common disease.

We bestowed this name on the syndrome for the following reasons: Clinically it is not unlike a pyogenic lesion and may well be mistaken for one, unless herpetic whitlow is borne in mind; there is no history of trauma and no contact with an established case of herpes or Kaposi's disease; finally, although it is a primary infection, glandular enlargement, lymphangitis, and constitutional symptoms are usually absent. In other forms of cutaneous herpes[2–4] there is trauma or dermatitis, and known exposure to herpetic stomatitis or Kaposi's eruption. On this basis the vast majority of herpetic whitlows would be missed.

Since herpetic whitlow is a primary infection, it can occur only in people with no antibodies to herpes. Reinfection does not occur and the injection of live herpes virus intradermally will not produce such lesions in people possessing antibodies. Recurrences are, however, common—as with other forms of primary herpes.

This relatively minor, but painful, illness is of special interest to the medical, dental, and nursing professions. They are most exposed to infection, and with improved hygiene more and more young adults can be expected to be without antibodies. Of those who are both susceptible and at risk a high proportion will develop the syndrome. The treatment, of course, differs radically from that of pyogenic whitlows.—We are, etc.,

H. STERN. D. M. MILLAR.
S. D. ELEK. H. F. ANDERSON.
Department of Bacteriology, St. George's Hospital Medical School, and The Hand Clinic, St. George's Hospital, London S.W.1.

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SIR,—Your timely annotation (September 9, p. 696) should serve to draw attention to this condition, which is by no means rare in nurses, especially those who

encounter the virus for the first time when they are nursing a child with Kaposi's varicelliform eruption due to herpes simplex virus: but the risk is neither confined to the skin wards nor to the nursing of children. Herpes simplex eruptions, usually on the face but occasionally more widespread, are a common sequel of neurosurgical operations, especially those in which the trigeminal or auditory nerves are interfered with, and nurses who have to look after these patients are also liable to develop herpetic infections of the hands if they have not met the virus before. Herpetic infection of the skin of the hands is particularly unfortunate, as recurrences may be frequent and the sufferer is liable at any time to develop secondary infection with the common pyogenic organism, possibly leading to cellulitis, lymphangitis, or carbuncles.

It may be asked why the risk of hand infection is so much greater for those who have the nursing of these patients, when labial herpes in other patients is not particularly liable to give rise to infection of the hands in those who nurse them. I think the answer is not so much that the strain of virus is particularly vicious (although there is no evidence either way), but that small children and unconscious or helpless patients need more nursing care, and the opportunity for intimate as well as repeated exposure to infection is correspondingly greater. It is not an uncommon experience to find that probationer nurses are particularly liable to develop staphylococcal lesions on the forearms and hands when they have to nurse small children with such lesions. Such infections are far less frequently seen in nurses later in their training when a fairly solid immunity develops as a result of repeated exposure to the common strains of staphylococci met with in hospitals. If the same holds true for herpes, it may be necessary to consider whether nurses liable to exposure should have the serum antibody titre against herpes virus estimated before working in wards where such risk is high. Those without any antibody might have to be excluded from these wards until they acquire some immunity in the more usual manner.—I am, etc.,

Dermatological Department,
The Hospital for Sick Children,
London W.C.1.

E. J. Moynahan.

Female with Mild Haemophilia

Sir,—We have reported in your journal (June 29, 1957, p. 1494) the case of a young adult female with a coagulation defect due to insufficient factor VIII (A.H.G.) and a family history of haemophilia, a maternal uncle, two male cousins on the mother's side of the family, and the patient's own brother having a severe degree of classical haemophilia. The patient's mother gave a history of bleeding for two weeks after dental extractions and also of menorrhagia, though her blood level of factor VIII was normal.

The patient herself, though only mildly affected, bled dangerously after abortion and subsequent hysterectomy. She had an apparently normal child whose blood, when examined at the age of 14 months, showed a reduced concentration of factor VIII (17%) which was of the same order as his mother's (18–25%).

At the time this low reading, though based on a single sample, formed the basis of a theory we put forward about the inheritance in this family. The child's plasma was retested when he was aged 6 years, and the level of factor VIII found to be 97%. It must be concluded that the first assay result was erroneous and the interpretation based on it wrong.

Presumably the patient is a carrier of haemophilia in whom the gene is only partially recessive.—We are, etc.,

Keith Taylor.
Rosemary Biggs.

Nuffield Department of Clinical Medicine,
The Radcliffe Infirmary,
Oxford.

Pyrimethamine and Polycythaemia Rubra Vera

Sir,—The paper by Drs. D. E. Pegg and H. T. Ford (September 2, p. 617) brings out a number of interesting points concerning the control of polycythaemia rubra vera. The word "control" is used advisedly, for in the management of this condition this is not necessarily synonymous with treatment. Because of the chronic nature of their condition, patients with polycythaemia become very well known to the department which they attend, and their treatment gives full scope for the art as well as the science of medicine.

There are two quite distinct aspects: firstly, there is the mathematical and purely arbitrary control of the circulating red cell mass for which we find it a convenient "rule of thumb" that the packed cell volume should not be permitted to rise above 55%. (Reference only to the haemoglobin concentration can be seriously misleading, as the M.C.H.C. may be low and a raised haematocrit can be present with an unremarkable haemoglobin level.) Periodic venesection and/or the use of ^{32}P seems to be the most convenient regimen. Secondly, however, there is the treatment of the patient as an individual. The many little complaints which they suffer tend to increase in importance as time passes: transient headaches, a subjective feeling of oppression, erythromelalgia, epigastric discomfort, skin irritation, and, not infrequently, non-specific querulousness. Such symptoms often respond to venesection, irrespective of the packed cell volume, and we generally leave it to the patients to request this if they know it affords them symptomatic relief.

Pyrimethamine frequently causes epigastric discomfort at the therapeutic level and it is for this reason that we abandoned its use, although it is a quite effective agent for depressing erythropoiesis. Occasionally, for no reason that we could discern, patients on long-term pyrimethamine therapy in the 50–75 mg. range developed an unpleasant taste in the mouth. There is one circumstance, however, when it might prove a most useful tool. Towards the end of the course—and this may now be after seven to ten years' surveillance—venesection may become difficult, especially when minor superficial phlebothrombosis becomes a nuisance and the allocation of 20–25 mc. ^{32}P spread over the years makes further use of this radioactive preparation unwise. At this point an effective oral therapeutic agent is a great assistance. In such instances tretamine is probably preferable, for it is more effective in its depression of the white cell mass which is usually raised at this stage, and in the long run patients tolerate it much more readily. I would agree that pyrimethamine is not a difficult drug to use for the stabilization of polycythaemia rubra vera, but in view of these minor effects which can become so important to the patient I recommend that it is used only if other means are not ready available.—I am, etc.,

Haematology Department,
St. George's Hospital,
London S.W.1.

J. L. Stafford.

Immunization Schedules

SIR,—The memorandum on routine immunization against infectious diseases (September 16, p. 763) is a shocking exhibition of ministerial inhumanity. Needle-pricks are an occupational hazard of being a baby, and should be cut to a minimum. The memorandum could be discussing injecting a cheese, not a live, sentient human being. There is no mention of infantile reactions to large needles repeatedly being thrust into him, of terrifying white coats, or of an antiseptic atmosphere of pain linked in the child's mind with clinics.

There is an excellent psychological reason why small-pox vaccination should be done at 10–12 weeks, and that a fortnight later first triple antigen (diphtheria–pertussis–tetanus) should be given and repeated at monthly intervals until completed at 6 months. It is that if these injections are delayed further the child becomes aware of why he is at the clinic or surgery, and receives a profound and lasting impression of pain associated with white coats and doctors, and which may upset him for years, even for life. I know that, fortunately, not all children are like this: but a great many are. Indeed, this impression may be the greater in the child's mind if the clinic has a poor psychological approach, where the doctor faces the baby with a syringe poised, and the babies or children are possibly in a queue in line. My own practice is never to let the baby see the needle. The baby is prone over the mother's knee, and the latter keeps one arm over his back and one over his legs, firmly. I use a needle made to my own specification which is a quarter of an inch (6.4 mm.) long and of 17 gauge. This can be inserted into the buttock rapidly, safely, and painlessly. To face a baby armed with a needle, to nip the skin of his left arm, and slowly to stick the needle in to the required depth is mediaeval torture. The method I use is effective enough, for I have never had a case of diphtheria or tetanus since the beginning of triple antigens, and very little, mild, whooping-cough, in vaccinated children. I think the Schedules P and Q are academic. Poliomyelitis vaccination has to be done later, from 7 months.

Perhaps the authors of the memorandum have never heard of Gesell, but his book is worth quoting[1]:

"At 4 weeks the neonatal period is drawing to a close. With each succeeding week the infant moves more deeply into his domestic environment. At 16 weeks he is already graduating from the cosy confines of his bassinet. He has longer and better defined waking periods; he may even demand social attention by fussing. His traits of individuality are becoming more obvious. Conflicts with excessive and untimely environmental pressures arise. His acculturation is well under way."

It is our business as doctors not to condition the child to hate us.—I am, etc.,

Rothwell Haigh, Near Leeds, Yorkshire. C. E. GOLDSBOROUGH.

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Sensory Loss in Poliomyelitis

SIR,—The interesting and important observation of Dr. R. V. Walley (July 1, p. 33) prompts me to add some of our own experiences in regard to this unusual finding. We have been working with poliomyelitis since 1952 and fully agree with Dr. Walley that "pains in the back and leg muscles are the rule, and loss or even alteration of sensation is extremely rare."

Since 1952–61 more than 1,600 polio cases have passed through the ward. Among them we came across two cases of hypaesthesia, one of them with complete sensory loss. In the latter a wide area of sensory loss was evident on the abdomen, back, and hips, with no response to marked painful stimuli such as pinching or pricking. Our consultant neurologist could find no explanation for this other than the underlying disease of polio. The unequivocal clinical diagnosis of polio (a flaccid paralysis of the lower legs, general adynamia, head drop) was confirmed by the finding of virus of polio type I in the stool and a rising complement-fixation titre in the blood.

Indeed, sensory loss in poliomyelitis is an unusual feature in the symptomatology. As we know, the usual sensory change in polio is hyperaesthesia, which, according to Mueller,[1] is an "early pathognomonic symptom." In the discussion on the clinical picture of poliomyelitis at the First International Poliomyelitis Conference, Ritchie Russell[2] states that he was impressed by the fact, which was emphasized by St. Thieffry, that the occurrence of poliomyelitis without pain is "quite exceptional." In a series of 100 described cases only two had no pain. Though the absence of pain is a rare feature, the presence of sensory loss is definitely an exceptional phenomenon.

It becomes more evident all the time, in our opinion, that poliomyelitis is not a monolithic disease as it seemed for a long time and as it has been stated in the textbooks for many years, but a most varied one, very often "bizarre,"[3] "*déroutante*,"[4] or even "erratic and unpredictable."[5] Serious authors, amongst them Weinstein,[6] do not consider the disease confined strictly to the nervous system, and think that it is rather a *diffuse* one which embraces in its clinical features other systems such as the vascular, the myocardium, the lymph nodes, the gastrointestinal tract, and others. We have drawn attention to some unusual features of the complex picture of poliomyelitis in Israel as observed in the last years.[7 8] It is not surprising therefore that we are often tempted by the popular cliché that "the more we learn about poliomyelitis the less we know about it."—I am, etc.,

Department of Paediatrics, Tel-Hashomer Hospital, Israel. Y. ROTEM.

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Medical Aid to Developing Countries

SIR,—How very well, and how very warmly, Dr. Bruno Gans (September 16, p. 767) has stated his views. As he so rightly asserts, there is an imbalance in medical and nurse training. Surely there is a wrong emphasis also in the mode and place of training of medical graduates and nurses from overseas. Many of them come for training, but especially in obstetrics and general surgery they remain to do a job. They remain to obtain experience not open to them overseas. Young overseas graduates exert their most enthusiastic efforts

for years in the service of hospitals in Britain. They spend in this country these years of perhaps their greatest effort because they are keen to work and anxious to learn, but above all because, as Dr. Gans points out, their special knowledge may find little scope in overseas territory.

Recently, in an overseas appointment as a surgeon, I laid the foundations of the complicated administrative and organizational network to establish a nursing training school. This was merely to extend, as a natural outcome, the systematic instruction and lectures I gave in my spare time. Nevertheless there was much routine surgery. In this I worked alone. The hazards and anxieties of major, and especially emergency, surgery were a solitary burden which I would gladly have shared. It seems to me that consultants are, quite naturally, too firmly established to spare a year or more away from their work. Senior registrars are not rooted or established in quite the same way but are perfectly capable of training registrar level specialists in overseas territories.

As tradition grows in new nations, it is the hope of the patients who cannot travel that the training of specialists will be nearer to them than far-away England to which so many graduates now travel.—I am, etc.,

Epsom District Hospital, Epsom, Surrey. NOEL JACKSON.

Lignocaine with Adrenaline

SIR,—Thoughts similar to those of Drs. D. D. Craig and C. J. Levy (September 23, p. 826) must have occurred to many. I have raised the question with a manufacturer who produces varying strengths of lignocaine with adrenaline 1 in 80,000; the reply was that adrenaline in a solution weaker than 1 in 80,000 becomes unstable unless the *p*H of the solution is altered greatly. Such a solution might damage the tissues and cause considerable pain when injected into a conscious patient.

In order to reduce the concentration of adrenaline to a safer level it is convenient to dilute one part of the solution of lignocaine 2% with adrenaline 1 in 80,000 with three parts of normal saline to make a solution of lignocaine 0.5% with adrenaline 1 in 320,000. This can be done most simply by pouring the whole contents of a 20 ml. bottle of lignocaine 2% with adrenaline into a sterile standard medicine glass, which providentially holds 80 ml., and filling it to the brim with the normal saline. This method of producing a satisfactory concentration of lignocaine and adrenaline, by avoiding possible arithmetical errors and mistakes in measuring small volumes, seems safer than adding adrenaline 1 in 1,000 to a solution of plain lignocaine. It also ensures that no partially used and possibly contaminated bottles of local anaesthetic are retained in the operating theatre.—I am, etc.,

R. CAMPBELL CONNOLLY.

Royal National Orthopaedic Hospital, London W.1.

Plantar Warts

SIR,—I was very pleased to read Dr. C. F. V. Vickers's article (September 16, p. 743) drawing attention to the very valuable method of treating plantar warts with formalin soaks. He mentions that I described a different technique of using formalin, but he did not give details of this. The method I use is to soak in 3% formalin solution a cotton-wool pad slightly larger than the area of wart to be treated. This is applied to the wart with a piece of adhesive strapping, kept on overnight, and removed in the morning. The desired effect of the treatment is the same as when using the 20-minute nightly soaks—namely, to produce a hardened area of skin—and, as Dr. Vickers mentions, in some cases it is necessary to increase the strength of the formalin solution. The advantage of the overnight method is that it obviates the 15–20 minutes nightly soaking and therefore is much easier to carry out.

I reported[1] that cures could be expected in all plantar warts in one-third to one-half of the cases. Dr. Vickers has a success rate of 80% in warts under 1 cm. diameter using the nightly soaks. It is, however, extremely difficult to compare results of treatments of plantar warts, and the effect of suggestion plays an important part. My results refer to random cases treated by different doctors in the busy out-patient clinics and not to a personal series.

Provided the area of skin is properly "formalinized" I do not think it matters which method is used, but the one I described is much easier for the patient to manage.—I am, etc.,

Bristol. ROBERT P. WARIN.

REFERENCE

[1] Warin, R. P., *Practitioner*, 1958, **180**, 371.

Patients with Trophoblast Tumours Wanted

SIR,—Dr. I. Gordon's query (September 16, p. 768) concerning the effect of AzUR upon different parts of the conceptus and its derivatives cannot fully be answered until our observations in mice have been extended and corresponding investigations carried out in human subjects. However, Dr. Gordon's apprehension of dangers inherent in a treatment which "produces a mole" can be allayed both by our own observations and by the general pathological characteristics of hydatidiform mole and chorion carcinoma.

Firstly, the formation of the relatively structureless mole in the mouse under the influence of AzUR is a purely transient response and is terminated by autolysis leading to the complete resorption of both the foetus and its trophic apparatus. Secondly, the short-lived mole is equivalent to a carneous mole, which is biologically inert compared with a hydatidiform mole or a malignoma derived from trophoblast. Lastly and most important, even if a carneous mole were to be produced, it would be a benign and desirable alternative to the malignant condition for which we propose the experimental use of AzUR.—We are, etc.,

MARGARET A. SANDERS.
B. P. WIESNER.
JOHN YUDKIN.
DAVID SAVAGE.

Department of Nutrition, Queen Elizabeth College, University of London.

Headache and "Eyestrain"

SIR,—I was most interested to read Dr. W. L. Cooper's letter (September 9, p. 710). Some time ago, on the advice of Professor R. D. Troutman, of New York, I obtained a space eikonometer, made by the American Optical Co., primarily to investigate the residual aniseikonia occurring in cases of uniocular aphakia corrected by anterior chamber implants. I found[1] that the average difference in image size was +2% in favour of the operated eye with a range from 0% to +9%. These patients did not complain of diplopia nor of

headaches. I have also conducted a small pilot experiment on normal persons—i.e., those not suffering from anisometropia—using a set of "size" lenses which magnify the retinal image of one eye without blurring it. First observations suggest that a difference in image size up to +5% is not ordinarily noticed, but then it does become noticeable until +8% or +9% is reached, when it becomes intolerable because of diplopia and not because of headache.

I recognize that there may be a wide limit of individual tolerance in respect of aniseikonia, but I cannot reconcile my own observations with Dr. Cooper's statement that "as little as ½% difference in size can be of dire discomfort to the patient." When binocular vision cannot be attained with spectacles because of aniseikonia (as in uniocular aphakia or uniocular high myopia) a contact lens should be tried, and if this fails recourse may be had to an intra-ocular lens implant which may succeed in bringing the disparity between the image sizes to within the 5% which I believe to be sufficient for easy tolerance in most cases.—I am, etc.,

Westcliff-on-Sea. D. P. CHOYCE.

REFERENCE

[1] Choyce, D. P., *Lancet*, 1961, **2**, 165.

Survival after Cerebrovascular Accidents

SIR,—Dr. David C. Wallace (September 23, p. 831) is correct in assuming that the patients on whom our prognostic survey was based (July 8, p. 73) were receiving 1 mg. of "dindevan" (phenindione). I am, however, unaware of any cogent evidence that this dose has any influence upon the coagulation mechanism of the blood. It has been extensively used not only in our own trial but also in the M.R.C. trial of anticoagulant therapy in cardiac infarction.[1] I think, therefore, it is reasonable to regard these patients as constituting an untreated group.—I am, etc.,

Institute of Neurology, University of London. JOHN MARSHALL.

REFERENCE

[1] *Brit. med. J.*, 1959, **1**, 803.

Advertising and Teenage Behaviour

SIR,—I fully support the views expressed (September 16, p. 769) by Dr. M. E. M. Herford. I am myself to-day writing to the Advertising Inquiry Council as he recommends. Chief constables from all parts of England report that in 1960 there was a large increase of offences by teenagers, many associated with drinking or driving (or both). The Minister of Transport makes earnest appeals to all to keep drinking and driving apart, but is this good advice likely to be followed when nearly everyone is a drinker and a driver? With the increased tempo of modern traffic "borderline drivers," which the Americans call "fringe-drivers," are a grave danger on our roads. In the case of accidents occurring late in the day they account for more than half the deaths, as I have been pointing out for several years. It is high time that we had a drink limit as well as a speed limit, particularly as the new Licensing Act will afford more opportunities for drinking.

The long discussions on the Road Traffic Bill in the House of Lords showed that even that august assembly is now prepared for more definite and drastic control of even slight intoxication when driving. We should hear no more of "borderline" cases after the Drew and the British Medical Association Committee's Reports.[1 2] In any new or refurbished Road Traffic Bill which is introduced, we as a profession should freely express our views that informed scientific opinion should be followed, rather than old-fashioned "rule of thumb" methods.—I am, etc.,

Leicester. N. I. SPRIGGS.

REFERENCES

[1] Drew, G. C., Colquhoun, W. P., and Long, H. A., *Effect of Small Doses of Alcohol on a Skill Resembling Driving*, 1959. Medical Research Council Memorandum No. 38. H.M.S.O., London.
[2] *Brit. med. J.*, 1960, **1**, 269.

Babies Prone or Supine?

SIR,—While on holiday this summer I spent a couple of pleasant afternoons in the Basle Zoo, interested by the way in which Achilla, the gorilla mother, handled her 8-weeks-old baby. This is only the third gorilla baby to be bred in captivity. The first was born in Columbus, U.S.A., in 1956; the second was Achilla's first infant named Goma, born in the Basle Zoo in September, 1959, and now a very lively 2-year-old.

Jambo, the new baby, spent most of her time clinging to her mother's torso. Sometimes, when her mother was walking around, the baby travelled clinging to a leg. From time to time Achilla put her baby down on the ground for short periods of exercise. First she spread a piece of sacking that she carried around with her, then she detached the baby from her and laid it down on the sack. She was very careful to put the baby down in the prone position, and on the occasions when it was wriggling and landed supine she picked it up again and turned it over.

This caught my attention at once, because a good many years of work with human mothers and infants have taught me that the human mother always uses the supine position for her baby unless given reasons for doing otherwise. Since head raising and control come earlier in the prone than in the supine position it would seem that the gorilla mother's choice is the wiser one, but it would also seem unlikely that human mothers could all be wrong. This difference of maternal opinion is interesting and deserves consideration.

It is well known that the higher the animal in the phylogenetic scale the longer is its immaturity and period of primary learning. Hebb[1] suggests that this period of primary learning concerns the establishment of sensory control of the association cortex of the brain and that the length of this period is directly proportional to the size-ratio of association cortex to sensory cortex. The ratio is higher in man than in the gorilla. The position the gorilla mother uses for her baby's exercise favours early motor activity which, indeed, develops stage for stage much more rapidly in the gorilla than in the human baby, as the most interesting account of Goma's progress given by Dr. Lang, the director of the Basle Zoo, and his colleagues makes clear.[2] The position the human mother chooses for her baby favours use of the sensory receptors, particularly the eyes, at the expense of early motor activity.

The human baby has much to learn that a gorilla can never know. It is fascinating to reflect that while the human infant lies on his back, apparently idly waving his useless arms and legs in the air, he is probably busy weaving himself a brain which is to be far more capable and adaptable than that of the up-and-coming young ape who is already struggling on to his hands and knees in a praiseworthy effort to get about.

We often encourage mothers to make more use of the prone position for their babies before they are able to turn themselves over, giving as our reason the earlier head-control in this position (see also *B.M.J.*, May 6,

p. 1304). Mothers frequently tell me that the baby objects to lying on his tummy and prefers his back. It seems highly likely that, once more, mother and baby know best.—I am, etc.,

Budleigh Salterton, Devon. NORA E. R. ARCHER.

REFERENCES

[1] Hebb, D. O., *The Organization of Behaviour: A Neuropsychological Theory*, 1949. Chapman and Hall, London.
[2] Lang, E. M., *et al.*, *Documenta Geigy: Series "Goma, Le Petit Gorille Bâloise."* J. R. Geigy, S.A., Basle.

Fusion of Labia Minora

SIR,—Having followed the correspondence on this subject in your columns, I was surprised to see a patient suffering from this condition recently.

The patient, a married woman of 70 years, was seen complaining of difficulty with micturition. Her main symptoms were frequency and incontinence of urine. Other doctors had seen her in the past and she had been diagnosed as suffering from congenital absence of the vagina. However, in her history she did insist that she had menstruated in her younger days. I found this very difficult to believe at first when I examined her. Her vagina appeared to be absent and her "urethral" opening consisted of a small pin-hole meatus.

On examination per rectum a uterus containing fibroids was felt. I watched her urinating, and instead of seeing a fine jet of urine, as one would have expected, it merely trickled on to her vulva and she had no control whatsoever. An intravenous pyelogram was normal, but in the plain *x*-ray two calculi were seen at the site of the bladder.

She was admitted for cystoscopy, and in the preliminary examination the true nature of her peculiar condition revealed itself. The labia minora had completely fused except for the small opening which was situated 2 mm. below the clitoris. This membrane was overlying the true urethra and her vagina. It was slit open and the normal anatomy was restored. Her hymen was still intact. In the vagina were two phosphatic calculi, one approximately 1.5 cm. in diameter. These must have developed as a result of the urine accumulating in her vagina before eventually being passed through the opening. Further questioning revealed that her marriage had never been truly consummated. Her menstrual cycle had been extremely irregular with prolonged periods of bleeding.

This condition, also known as synechia vulvae, is well described by Campbell.[1] Twenty-seven cases were described and it was concluded that the condition was congenital. Nalle *et al.*,[2] in a study of 110 cases, concluded that the condition is acquired and thought it to be the result of intrauterine inflammation or to result from post-partum inflammation with adhesion of the inflamed tissues.

The case described did not show any midline furrowing, ridging, or scarring, and the appearance was of one continuous membrane. Perhaps in the embryo the ridges at the lateral boundaries of the urogenital orifice which form the urethral folds, instead of remaining to form the labia minora in the female, had gone one stage further as in the male.

I thought that this case would be of interest to your readers. It illustrates how these patients can be mislabelled and can go through life with an abnormality which can be so easily corrected.—I am, etc.,

Saint Bartholomew's Hospital, Rochester, Kent. MITCHELL J. NOTARAS.

REFERENCES

[1] Campbell, M., *Urology*, 1954. Vol. 1, p. 485. Saunders, Philadelphia.
[2] Nowlin, P., Adams, J. R., and Nalle, B. C., *J. Urol. (Baltimore)*, 1949, **62**, 75.

Nuclear War

SIR,—We, as members of a humanitarian profession, feel that at this time of international crisis we should voice our protest at the possible destruction of humanity by nuclear weapons. We think that none of the world leaders wishes to have a nuclear war, but the longer this crisis continues, and the longer a final settlement is delayed, the more likely is an accidental beginning to nuclear war. Some physical or chemical accident could trigger off a weapon. Some finger poised, at this moment, near a button could quite easily have a psychotic brain behind it, and the firing of one nuclear device could start off the complete destruction of humanity.

After much thought and discussion we are of the firm opinion that the defence of any principle, either political or religious, does not warrant the total destruction of humanity.

Some of our colleagues who are of the same opinion feel that a protest such as this is of no value. But at least, in making it, we have exercised our right and duty as human beings to express our concern. We hope that members of the profession throughout the world may join us and do likewise.—We are, etc.,

A. A. CLARK.
J. W. COOK.
J. D. BANKIER.
H. BREBNER.
P. I. BROWN.
A. FAIRLEY.
T. E. S. FERGUSSON.
J. M. FLEMING.
W. J. GORDON.
J. W. JUNOR.
A. C. MACDONALD.
C. RANKIN.
ELIZABETH R. J. RITCHIE.
KENNETH B. SCOTT.
W. JEFFREY SCOTT.
W. TAIT.
A. C. THOMSON.

Dunbartonshire, Scotland.

Best Time for Lectures?

SIR,—It has always been a matter for regret to me that so many interesting and important lectures and clinical demonstrations take place in the late afternoon so that I could only attend by skipping evening surgery—an obviously impractical solution.

For the second year the B.M.A. has very commendably arranged a series of clinical meetings (September 23, p. 819) which I would very much like to attend. But once again they are arranged to start at 5.30 p.m. The average opening time for evening surgery is between 5 and 6 p.m., so cannot these discussion lectures be arranged for an earlier hour—say 2 or 3 p.m.? What do my fellow G.P.s think?—I am, etc.,

Wembley, Middlesex. M. SIFMAN.

POINTS FROM LETTERS

Grey Turner Memorial Lecture

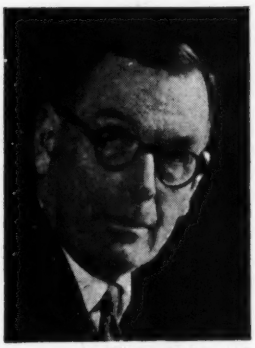
Dr. PHILIP H. WILLCOX (Windsor, Berks) writes: It is true that Lambert Rogers was Grey Turner's first reader in surgery at Hammersmith from 1934, but he had already left Hammersmith when I was appointed house-surgeon to Professor Grey Turner early in 1936, by which time Professor A. K. Henry had succeeded him as reader in surgery. Grey Turner's assistants included such names as Mr. G. Y. Feggetter and Mr. R. H. Franklin.

Obituary

Sir W. BENTLEY PURCHASE, C.B.E., *M.C.*, M.B. D.P.H.

Sir Bentley Purchase, H.M. Coroner for the Borough of Ipswich and lecturer in forensic medicine at University College Hospital and St. Thomas's Hospital Medical Schools, died as a result of an accidental fall from the roof of his house on September 27 at the age of 70. A prominent and admired member of the medical and legal professions he was formerly Coroner for the Northern District of London and also to the Queen's Household.

William Bentley Purchase was born on December 31, 1890, only son of the late Sir William Henry Purchase, and was educated at Bradfield and Sidney Sussex College, Cambridge. After taking his B.A. in 1911 he went to the London Hospital Medical College, where he qualified in 1914. During the 1914–18 war he served first as a "gunner" and then medical officer and was awarded the *M.C.* in 1917 and the Order of the White Eagle of Serbia in 1921. On his return to London he studied at University College Hospital and graduated M.B. at Cambridge in 1921, having taken the D.P.H. there in the previous year. He also read Law and was called to the Bar in 1919 as a Member of the Inner Temple, where he practised until 1930, being Treasury Counsel at the County of London Sessions (1924 to 1930) and appearing in, among other cases, the Croydon arsenic case. The period during which his work brought him into most prominence was when he was sitting as Coroner at St. Pancras (1930 to 1959), where he was closely associated with the late Sir Bernard Spilsbury. He was appointed C.B.E. in 1949 and knighted in 1958.



[*Elliott and Fry, Ltd.*

Purchase was a man of enormous energy and catholic in his interests, the only consideration in his mind being to produce something worth while, as can be seen from the varied duties that he undertook—including being secretary of the Coroners Society, consultant to the War Office on chemical warfare, a member of the Royal Commission on Abortion, a member of the board of governors of University College Hospital, chairman of St. Helen's Hospital Management Committee, a member of the Board of Advanced Studies in Medicine of the University of London, lecturer in civil law for the Supply and Accountant Officer courses of the Royal Navy, and lecturer in forensic medicine at the Royal Free Hospital Medical School (to the Student Union of which he used to give his lecture fees). He wrote much, mostly in connexion with coroners and legal medicine, being the author of *Practical Forensic Medicine* (jointly), *Aids to Forensic Medicine* (13th edition), and contributing to Halsbury's *Statutes of England*. He edited Lushington's *Affiliation and Bastardy*, and, with H. Wollaston, *Jervis on Coroners* (9th edition). Although giving some indication of his work, this does not really do full justice to Purchase, for he could be truly included in that rare category of great men whose known activities represent only a small part of what they contributed to medicine, the law, and their country. He was far too modest and discreet to tell it himself. Glimpses were revealed when he talked about the part he played in the famous wartime incident of "the man who never was," but even these activities were small in comparison with the personal acts of kindness which he performed. For essentially he was a kind man—no witness in his court was treated with other than the utmost courtesy and nobody who had a genuine personal problem ever left him without help. This was coupled with an immense loyalty to those who worked for him, a characteristic which nevertheless was never overdone should anybody do "an act" of which he ethically disapproved.

His outspokenness required a courage few can muster; he had no hesitation in saying what he thought. At the same time he never let his prejudices interfere with appreciation of something well done. This was well shown by his disapproval of any attack on Spilsbury in the later part of his career, and although still appreciating the technical ability of the critics he was quite unforgiving concerning the merit of the attack. This was probably the clue to his character, a strong sense of loyalty and generosity with an inflexible ethical standard. It was a unique experience to hear him in court cross-examining so-called experts in their own subject from his almost inexhaustible store of knowledge. It was perhaps for this reason that those who knew him experienced no surprise at the manner of his death—typical of a man who insisted on doing things himself because he knew he could do them better than most and hence stimulate those around him to excel themselves.

Legal medicine certainly owes him a great debt and medicine itself much for his influence on the coroner system of the country and for his other activities, both official and unofficial.

He leaves a wife, son, and daughter, to whom we offer our sincere sympathy.—F. E. C.

CLIFFORD E. ROBERTS, O.B.E., B.M., B.Ch. F.R.C.S.Ed., D.T.M.&H.

Mr. Clifford E. Roberts, who was medical superintendent at Hammersmith Hospital, died suddenly some days after an operation on September 25, at the age of 61. He had been at Hammersmith for only three years, but had come with a distinguished career behind him.

Clifford Ellis Roberts, who was born on November 11, 1899, served in the first world war before going up to Oxford as a medical student. He completed his training at the London Hospital, taking both the Conjoint Diploma and the B.M., B.Ch. degrees in 1925. He did his resident appointments at the London and Poplar Hospitals and in 1927 joined the Colonial Medical Service in Uganda. He took the D.T.M.&H. and the Certificate of the London School of Tropical Medicine (with Distinction) in 1930 and was promoted district medical officer. As well as being medical officer to the European and Asiatic hospitals in Uganda, he was for a time acting surgical specialist and tutor in anatomy and surgery at the Medical School in Mulago. As a sequel to this he took the F.R.C.S.Ed. in 1936, and in 1939 was transferred to Zanzibar as a specialist officer. During this period of his career he contributed original papers to the *East African Medical Journal*. Having been honorary secretary and president of the Uganda Branch of the B.M.A., he was later president of the Zanzibar Branch.

During the second world war he served with the East African Army Medical Corps and was surgeon first to No. 2 Casualty Clearing Station and later to No. 6 Hospital at Mombasa, to which he became O.C. He was ultimately O.C. of the Surgical Division, No. 1 Hospital, Nairobi. He then transferred to South-east Asia Command and went to Ceylon as commanding officer of the Zanzibar Field Ambulance and served in Assam and Burma, being mentioned in dispatches. Demobilized in 1945 at the request of the Zanzibar Government, he was appointed O.B.E. in the same year. He acted for a time as Senior Medical Officer in Zanzibar and was a member of the Legislative and Executive Councils until he retired for family reasons, when he was awarded the Brilliant Star of Zanzibar.

Having left the Colonial Medical Service he joined the Ministry of Pensions as surgical officer at Musgrove Park

Hospital, where he became senior medical officer in charge in 1949. In 1952 he was transferred to Chapel Allerton Hospital as medical superintendent, making a lasting impression there because his professional competence was combined with an exceptional personality. He came to Hammersmith in 1958: it was a difficult appointment, for medical administration did not then rank as high in lay circles as it had done twenty years before. But again his calm competence, his kindliness, his understanding of people, his willingness to listen and to help impressed everyone, lay and medical alike. He was such a nice person. Maybe no one is irreplaceable, but there are some, a few, whom everyone wishes could still go on, and of that small and desirable company "Dr. Roberts" was a conspicuous member.—C. E. N.

A. T. A. JURASZ, M.D., Hon.F.R.C.S.

Professor Anthoni Jurasz died suddenly in New York on September 20 in his 79th year. He was dean of the Polish School of Medicine established in Edinburgh in the early days of the second world war.

Sir Sydney Smith writes: Anthoni Thomas Alexander Jurasz was educated at Heidelberg, where his father was professor of laryngology, and there obtained the degree of Doctor of Medicine in 1907. He later became professor of surgery at the University of Poznan, where his father, in retirement, had undertaken the organization of a laryngological clinic. On the outbreak of the second world war he joined the Polish Medical Corps and was captured by the Germans. Making his escape to France, he came on to Britain, being finally posted to Scotland with a great number of his compatriots. In the Polish Army thus posted there was a great excess of medical men, many of professorial rank, who were gradually deteriorating owing to the dearth of medical work. In addition to these medical officers there were many senior medical men as well as numbers of medical students in the ranks. Jurasz took the matter up with the Army authorities and with the University of Edinburgh, and after a great deal of negotiation, in which he played the leading part, the University of Edinburgh agreed to provide facilities first for postgraduate training for the Polish medical officers and later a complete system of training for their medical students. The Government of Poland agreed with the University to give the Polish Faculty of Medicine power to examine and give degrees in medicine and surgery which would be recognized by the Polish Government for medical registration in Poland.

At that time Poland had been overrun by the Germans and the universities systematically destroyed. The idea was to get a complete school of medicine properly equipped so that on the completion of hostilities the whole school—teachers, scholars, and equipment—could be transferred to Poland and start work at once. This was not to be, owing to political developments which had not been foreseen.

Jurasz, as the first dean of the Polish Faculty, carried out all the preliminary work of arranging class teaching and hospital practice, and never was there such a dynamo of energy. He held the chair of surgery in the Polish School and was elected an Honorary Fellow of the Royal College of Surgeons of England in 1942. In addition to his administrative work he was the prime mover in the establishment of the Paderewski Hospital for the treatment of his compatriots and the training of Polish students. Further, he found time to play a leading part in the social life of his students, and became the trusted friend of a great number of his Scottish colleagues. By 1946, when the school was closed, 228 students had received their M.B. degree and 19 had proceeded to the M.D. Professor Jurasz then went to the United States and practised in New York until his death. He paid a fleeting visit to Edinburgh in August and seemed as full of vigour and fun as of yore, and we were all stunned to hear of his death shortly after his arrival back in New York. He is survived by his wife, to whom we extend all our sympathy.

J. F. MacCARTHY, M.B., Ch.B.

Dr. J. F. MacCarthy, who held an appointment as a chest physician in Sheffield, died on September 11 when on holiday in Ireland. He was 51 years of age.

Jeremiah Francis MacCarthy was born in Cork and after studying medicine there he graduated M.B., Ch.B. in 1935. He came to Sheffield in the same year and after holding house appointments at the Sheffield Royal Infirmary he became assistant medical officer at the City General Hospital, Sheffield, and later deputy medical superintendent at Kilton Hall Hospital, Worksop. He joined the R.A.F. in 1938 as a regular officer and served most of the war years in India and Burma, leaving the Service in 1946 with the rank of Wing Commander. After a refresher course at the City General Hospital, he entered the Sheffield tuberculosis service in 1947 and worked in Sheffield as a chest physician until his death. He held resident appointments at Winter Street Hospital and Crimicar Lane Sanatorium and later worked at Nether Edge and Lodge Moor Hospitals, returning to Winter Street Hospital in 1960.

A most conscientious and devoted physician, he was a warm-hearted and kindly man who was held in high esteem by his colleagues, the nursing staff, and the many patients under his care. His courage, good humour, and devotion to duty, in spite of ill health in his later years, were an inspiration to those who had the privilege of working with him, and he will be greatly missed by all who knew him. The large congregation at a solemn requiem mass at St. Vincent's Church on September 22 gave some indication of the affectionate regard in which Dr. MacCarthy was so widely held. Our deep sympathy is extended to his widow and children.—W. J. W.

R. Y. STONES, O.B.E., *M.C.*, M.D., M.R.C.P. F.R.C.S.Ed., D.P.H., D.M.R.E.

The death of Dr. R. Y. Stones at Mengo Hospital, Kampala, on September 16, at the age of 80 years, closes a medical career of great distinction and usefulness.

Robert Yelverton Stones was an outstanding student at the London Hospital, and after graduating M.B., B.S. in 1907 and gaining the D.P.H. in 1908 and the F.R.C.S.Ed. in 1910 he sailed for Africa in 1911 as a missionary of the Church Missionary Society. He first worked at Iyi Enu Hospital, Nigeria, and in 1913 was transferred to Old Cairo Mission Hospital in Egypt. During the first world war he was commissioned in the R.A.M.C. and served first in the near East and then in German East Africa, being awarded the Military Cross. At the end of the war he began missionary work again in Tanganyika, doing outstanding service in the famine at Dodoma in 1919. From Dodoma he went to Maseno in Kenya, near Lake Victoria, where he founded a hospital with Red Cross funds. Continuing to win academic honours, he proceeded M.D. in 1918 and took the M.R.C.P. in 1925 and the D.M.R.E. in 1930.

In 1924 he came to Uganda and joined Dr. (afterwards Sir Albert) Cook at Mengo Hospital, Kampala, the mission hospital which Cook had founded in 1897. Here he worked till 1939, latterly as medical superintendent, and was appointed O.B.E. in 1938 for his services. He returned to England in 1939, but could not reconcile himself to a quiet life at home. He joined the R.A.M.C. and was in Malta during the siege and stayed on afterwards for a time in charge of the King George V Hospital for Merchant Seamen.

After the death of his wife he felt the urge to return again to his work in Africa, and revisited first Nigeria and then Uganda. Although now in his seventies he resumed work at Mengo Hospital for a time, finally concentrating on ophthalmology, always one of his great interests. He was seeing patients at his eye clinics until the onset of his last illness. Always keenly interested in the work of the

Order of St. John of Jerusalem he was appointed first a Serving Brother and then an Officer of the Order. In his younger days he was a vigorous tennis player and swimmer, and also a pioneer motorist, having been a driver for at least 50 years.

Quiet and reserved, and a most modest man in spite of his professional distinctions, he only wished to use his talents for the greatest good, wherever he was, for he was a true and humble Christian. He was keenly interested in the advancement of African doctors and longed to see them taking their place in the different hospitals in which he had served. His uncomplaining patience in his last illness was characteristic of him, and it was fitting that he should end his days in the country for which he had done so much and in the hospital he had served for so long.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in August was 85, compared with 90 in the previous month and 94 in August, 1960.

The numbers of cases of industrial diseases in the United Kingdom reported during August were as follows: lead poisoning 2, aniline poisoning 2, toxic jaundice 1, compressed-air illness 2, anthrax 1, epitheliomatous ulceration 10, chrome ulceration 48: total 66. There were no deaths.

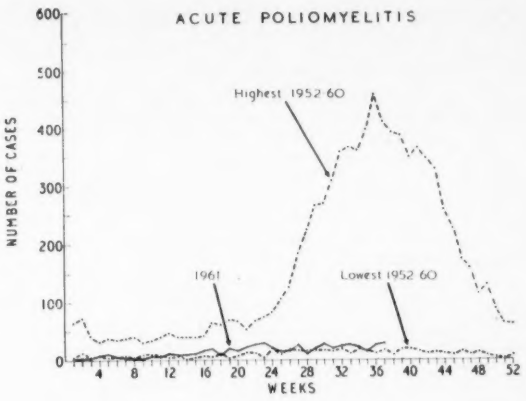
Infectious Diseases

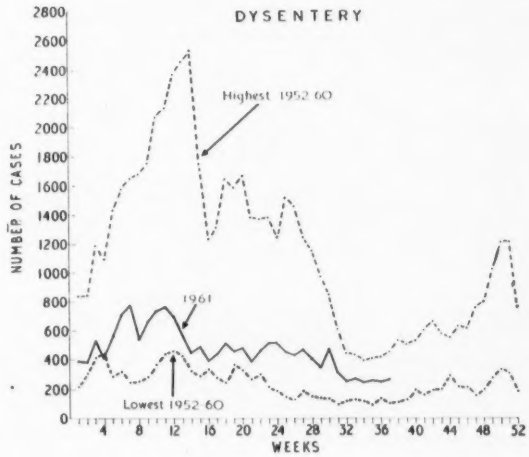
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

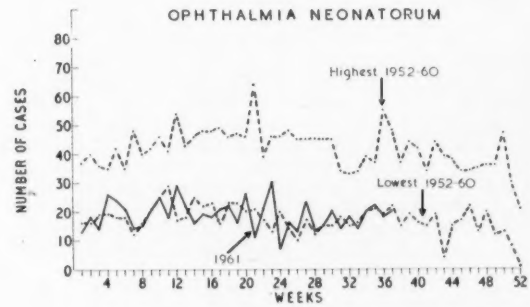
	Week Ending Sept. 16	Sept. 23
Dysentery		
Lancashire	76	**93**
Liverpool C.B.	19	**25**
Worsley U.D.	12	**14**
Yorkshire West Riding	21	**44**
Leeds C.B.	12	**11**
Dearne U.D.	0	**11**
Glasgow	91	**83**
Dundee	33	**27**
Edinburgh	22	**21**
Acute Poliomyelitis		
Lancashire	16	**17**
Liverpool C.B.	6	**4**
Manchester C.B.	0	**3**
Food Poisoning		
Lancashire	73	**67**
Blackpool C.B.	35	**32**
London	29	**38**

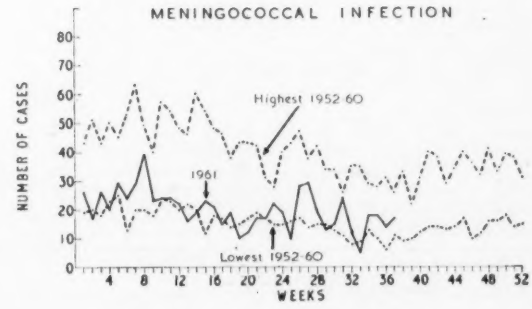
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 16** (No. 37) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	2	0	0	0	1	2	2	2	0	
Dysentery ..	264	32	207	3	3	307	46	190	16	3
Encephalitis, acute	7	0		1		2	0	0	0	1
Enteric fever:										
Typhoid ..	1	0	1	0		2	1	0	0	
Paratyphoid ..	1	0	1(B)	0	1(B)	13	1	0	0	
Food-poisoning ..	227	29	50	1		196	26	10	9	
Infective enteritis or diarrhoea under 2 years				17	28				21	20
Measles*	1,043	47	16	37	21	1,087	54	44	4	5
Meningococcal infection	17	0	5	1		16	0	25	0	
Ophthalmia neonatorum	20	2	3	0		23	0	4	0	
Pneumonia† ..	84	3	80	4		123	6	101	3	
Poliomyelitis, acute:										
Paralytic ..	24	2	0	} 1	2	{ 13	7	0	} 0	7
Non-paralytic ..	4	1	1			3	0	0		
Puerperal fever§ ..	169	35	8	1	1	127	10	14	2	
Scarlet fever ..	161	9	34	15	13	238	15	33	13	22
Tuberculosis:										
Respiratory ..	294	37	40	11		389	41	65	10	
Non-respiratory	46	5	11	14		47	6	8	3	
Whooping-cough	299	27	47	6	12	1,372	146	122	3	25

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0		0
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years	6	1	3	0	0	1	0	1	2	3
Influenza	7	0	0	0	0	3	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	357	39	13	13	0	389	36	16	15	3
Poliomyelitis, acute	2	0		0	0	0	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 50	{ 5	} 9	{ 1	1	} 44	{ 3	3	0	7
Non-respiratory		1		0	0		1	1	0	1
Whooping-cough	0	0	0	0	0	1	0	0	0	0
Deaths 0–1 year ..	283	26	29	9	14	276	24	21	9	8
Deaths (excluding stillbirths) ..	8,498	720	535	114	127	8,534	709	536	127	111
LIVE BIRTHS ..	15,367	1357	950	252	444	14,547	1248	931	257	342
STILLBIRTHS ..	291	23	28			294	20	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Attempt to Photograph Smallpox Patient

The alleged attempt by the representative of a newspaper agency to photograph a patient suspected to be suffering from smallpox in an isolation hospital was adjudicated by the Press Council last February. An appeal was entered against the findings, and further evidence, some of it tendered orally, was sifted by the Council, which has issued the following revised adjudication:

Dartford Hospital Management Committee complained that a photographer employed by John Topham, Ltd., of Sidcup, Kent, trespassed on a private road to get to Long Reach Isolation Hospital, Dartford, and there represented to the gate porter that he had permission to photograph a patient suffering from smallpox. Permission to take the picture had not been sought beforehand though the photographer was under the impression that it had been granted. The hospital authorities stressed the point that if he had entered the hospital the photographer might have become a grave danger to public health. The photographer denied that he told the gate porter that he had been authorized to enter the hospital to take pictures. He stated that he had no intention of entering without official permission. Mr. C. WINTOUR, editor of the *Evening Standard*, admitted that his newspaper had commissioned the agency to obtain picture coverage, but dissociated himself from the means it was claimed had been employed to obtain it. There was a conflict of evidence between the newspaper and the agency as to the precise instructions given. The Council condemned the effort to obtain a picture and recorded the opinion that the photographer should not have been sent to the hospital unless prior permission had been obtained.

Cheaper Drugs in Hospitals

The Ministry of Health has announced that contracts have now been placed for hospital supplies of tetracycline, chlortetracycline, oxytetracycline, chloramphenicol, and chlorothiazide manufactured in Italy or Denmark. This follows the Minister of Health's announcement that he would invoke the Patents Act, 1949, to obtain some drugs for the hospital service more cheaply than by the previous procedure (see *Journal*, May 27, p. 1522). The Minister states that the drugs ordered are of high quality, conforming in all respects to British standards. The claims of any patentees concerned will be considered and royalties negotiated as appropriate. All the successful tenderers are British companies, but none is a patentee or licensee.

A statement issued by the Association of the British Pharmaceutical Industry after the Ministry's announcement expressed fear that manufacturers in Britain would no longer be encouraged to maintain, let alone increase, their expenditure on research if hospital contracts for their most successful drug discoveries were to be awarded to unlicensed competitors. Further, the association believes the action of the Health Minister can only have an adverse effect on the industry's export trade, which is now running at 10% over the record figure of £44.4m. in 1960.

Gift to Middlesex Hospital Medical School

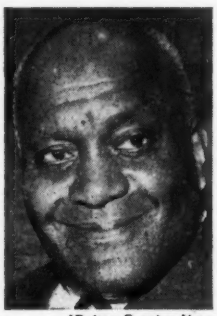
Sir BRIAN WINDEYER, dean of the Middlesex Hospital Medical School, speaking at the school's annual dinner at the Savoy Hotel on September 29, announced another magnificent gift from Lord ASTOR OF HEVER, chairman of the hospital and school council. To the £400,000 Lord Astor has already donated he has now added a further £200,000, and this will enable the new school begun in 1955 to be completed according to plan (see *Journal*, December 26, 1959, p. 1480). One of the remaining buildings to be constructed is a residential college for 175 students: this will be named after Lord Astor of Hever. Other speakers at the dinner were Mr. W. R. WINTERTON, who as chairman proposed the toast to the hospital and medical school; Dr. LINDA STANTON, senior Broderip scholar; and Professor C. A. KEELE, who proposed the health of the chairman.

Wellcome Trust Grants

The Wellcome Trust has made a grant of £100,000 for work on tropical anaemias and kindred disorders (see *Journal*, p. 948). Other major grants out of the total of £248,000 distributed by the Trust during the last half-year include £10,000 to Professor H. E. DE WARDENER to improve research facilities in the Department of Medicine at the Fulham branch of Charing Cross Hospital; £15,000 to Professor J. D. LEVER to purchase an electron microscope for the Department of Anatomy, University College of South Wales and Monmouthshire; and £40,000 to Professor H. O. SCHILD and others for the extension to the pharmacology building at University College, London, already announced in July. A five-year senior Wellcome Research Fellowship of £18,000 has been provided for Dr. KARLIS ADAMSONS in the Columbia-Presbyterian Medical Center, New York City, for studies chiefly concerned with the physiology of the newborn.

G.P. Installed as Farnworth Freeman

Dr. V. ST. CLAIR LUCAS, a native of Trinidad, who has been a general practitioner in Farnworth, Lancashire, for 40 years, was recently installed as one of the town's first two freemen.



[*Bolton Evening News*

Dr. Lucas, who is 68, qualified M.B., Ch.B. from Edinburgh University in 1917. He was medical officer at Farnworth's first-aid post during the last war, and having retired from general practice is now a headquarters section instructor and scientific intelligence officer in the North-west Region. He is a serving Brother of the Order of St. John of Jerusalem, and had been Divisional Surgeon of the Farnworth Branch of St. John's Ambulance Brigade until his retirement last year.

Medical Protection Society's Annual Report

The Medical Protection Society's *Sixty-ninth Annual Report of the Council for the Year Ended December 1960* describes the year as "one of outstanding progress . . . marked by a record number of new cases undertaken on behalf of members and by a further substantial increase in membership." The total membership at December 31 (figures for 1959 in brackets) was 36,858 (35,551); new members elected, 2,817 (2,325); net increase in membership 1,207 (1,063); new cases undertaken on behalf of members, 2,249 (2,210); accumulated funds, £222,556 (£207,525). Income exceeded expenditure by £15,035.

Medical Defence Union's Annual Report

In 1960 one out of every 16 members of the Medical Defence Union wrote for advice or assistance, and in addition about 4,000 telephone inquiries were dealt with by the secretariat; 2,837 cases were handled as against 2,703 in 1959. Total membership stood at 47,450, 2,425 being overseas members. The report points out that in spite of fluctuations during the last decade in the number of complaints made to the Medical and Dental Service Committees the percentage dismissed is surprisingly constant—65% to 77% of medical cases and 40% to 57% of dental cases. During the year income exceeded expenditure by £23,777. Indemnity payments amounted to £48,000—the largest sum the union has ever incurred by way of damages and costs in any one year. The union's total funds, including the Guarantee Fund, amount to £207,666; £947,550 has been spent since 1885 in advising and protecting members. The M.D.U. warns members of the dangers that may arise in the use of electrical equipment in the course of treatment.

King's College Hospital Medical School Dinner

The King's College Hospital Medical School annual dinner was held at the Savoy Hotel, London, on September 30 under the chairmanship of Dr. FRANK BROCKINGTON, of Camberley, Surrey. A good attendance of past and present members enjoyed the pleasures of reunion and reminiscence and listened to two speeches excellently suited to the occasion. Mr. HAROLD C. EDWARDS proposed the chairman's toast and Dr. Brockington replied. Mrs. Brockington was present in her own right as a King's graduate.

Responsibility for Nursing-Homes

A report published by the National Corporation for the Care of Old People, *Nursing Homes in England and Wales*, gives five immediate reasons for dissatisfaction with the methods by which public responsibility for nursing-homes is exercised: "Some establishments are run as nursing-homes and yet escape registration and inspection; voluntary homes may be exempt; the patients in many homes have few contacts with organizations and individuals in the local community; there is no formal method of ensuring that the proprietor or matron is a person fit to care for the infirm and sick; and finally the standard of amenities and staffing attained by a substantial number of nursing-homes is inadequate." The report suggests the lines along which legislative reform might be made, pointing out that the "existing legislation is extremely weak and anomalous." (N.C.C.O.P., price 7s. 6d.)

"Alcoholism"

The memorandum on alcoholism which was prepared by a joint committee of the British Medical Association and the Magistrates' Association and printed in the *Journal* in the spring of this year has now been reprinted as a leaflet with additions and corrections. Copies can be obtained free of charge from the Secretary of the Association, B.M.A. House, Tavistock Square, London W.C.1.

Road Safety Campaign

The Royal Society for the Prevention of Accidents has launched a road safety campaign with the slogan "Fit for the Road" which draws attention to the fitness of vehicles as well as of drivers. Special material has been produced for the campaign dealing with safety straps, braking and steering, first-aid, cycling, commercial driving, eyesight, and drinking. The B.M.A.'s recommendations on the maximum safe concentration of alcohol in the blood of a driver are included in the campaign leaflet, *Searchlight on Drink*.

Broadcast School for Australian G.P.s

The University of New South Wales is planning to broadcast through its own station, Radio University, courses designed to keep general practitioners in Sydney abreast of developments in medicine. It will offer lectures and discussions by medical teachers and research workers, talks by specialists from overseas, answers to doctors' questions, and book reviews. A committee is being formed to advise on the subjects to be covered and the times most suitable for broadcasting. Doctors will need to have their receivers slightly modified to hear Radio University.

Gift to St. Catherine's, Oxford

Dr. RUDOLPH A. LIGHT, who graduated in physiology from St. Catherine's Society, Oxford, in 1934, has given a block of American shares currently valued at £193,000 to the new foundation which is to take the Society's place—St. Catherine's College. Dr. Light was visiting surgeon in the Nuffield Department of Surgery at the Radcliffe Infirmary, Oxford, in 1958.

In Brief

▶ The Royal National Throat, Nose, and Ear Hospital's Hostel for Deaf Children at Castle Bar Hill, Ealing, was opened recently by the Minister of Health, Mr. ENOCH POWELL. The hostel will provide additional accommodation for the children who attend the hospital's Audiology Unit, and for their parents.

▶ A new ward block has been opened at the Royal Belfast Hospital for Sick Children. Twenty of the beds are

reserved for specialized surgery, and seven of them are in an air-conditioned annexe for patients undergoing plastic surgery.

People in the News

▶ Dr. G. E. GODBER, chief medical officer of the Ministry of Health, and Dr. LUTHER L. TERRY, Surgeon-General of the U.S. Public Health Service, recently addressed the American Hospital Association's annual meeting on "Public Health Planning—British and American Views."

▶ Professor J. N. DAVIDSON, F.R.S., of the Department of Biochemistry, University of Glasgow, delivered the Bottazzi Memorial Lecture on October 4 in Cagliari, Italy.

▶ Mr. F. W. M. PRATT, senior surgeon at the Willesden General Hospital, was given a retirement dinner and reception on September 15, at which presentations were made both by his hospital colleagues and on behalf of many of the doctors in Willesden and the surrounding area.

COMING EVENTS

London Medical Orchestral Society.—Rehearsals have started and will take place every Thursday, 7.45 p.m., Rutherford School, Penfold Street, off Edgware Road. Details at rehearsal or from Dr. H. ENGEL, 40 Warrington Crescent, London W.9.

Cambridge University School of Clinical Research and Postgraduate Medical Teaching.—Postgraduate courses for general practitioners, October 1, 1961, to July 31, 1962. Details from secretary, Medical School, Tennis Court Road, Cambridge.

West of Scotland Surgical Association.—Annual meeting, October 13, 3.45 p.m., Royal Faculty of Physicians and Surgeons, 242 St. Vincent Street, Glasgow. Details from Mr. H. WAPSHAW, Western Infirmary, Glasgow W.1.

Doctors' Window.—Dedication, Guildford Cathedral, October 22, 3 p.m., Sir ARTHUR PORRITT, P.R.C.S., Acting-President, B.M.A., will read lesson and lead doctors' procession to present window to the Bishop. Representatives of Royal Colleges, Master of Society of Apothecaries, President of College of General Practitioners, R.A.M.C., and other organizations will attend.

London School of Hygiene and Tropical Medicine Association.—Annual dinner, Waldorf Hotel, Aldwych, London W.C.2, November 21, 7 p.m. Dancing until midnight. Tickets (35s. each; guests permitted) from Miss K. M. SHAW, London School of Hygiene and Tropical Medicine, Keppel Street, London W.C.1.

Italian Society of Endocrinology.—First symposium on "Steroidal Phenol and Enol Ethers in Clinical Practice and Biology," Rome, December 11. Details from Symposium Secretariat, Istituto di Patologia Speciale Medica, Policlinico Umberto I, Rome, Italy.

NEW ISSUES OF SPECIALIST JOURNALS

The Journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

THORAX

Gastroplasty. J. Leigh Collis.

Development of the Intrasegmental Bronchial Tree: the Pattern of Branching and Development of Cartilage at Various Stages of Intra-uterine Life. U. Bucher and Lynne Reid.

Development of the Mucus-secreting Elements in Human Lung. U. Bucher and Lynne Reid.

An Analysis of 700 Cases of Carcinoma of the Hypopharynx, the Oesophagus, and the Proximal Stomach. B. T. le Roux.

An Assessment of Antibacterial Treatment Used Alone or in Association with Surgical Operation in the Treatment of Pulmonary Tuberculosis. J. R. Edge, W. H. Helm, M. R. Geake, and R. L. Ward.

The Pathology of Asbestosis, with Reference to Lung Function. Brian E. Heard and Roger Williams.

Pulmonary Function in Kyphoscoliosis. Colin G. Caro and Arthur B. DuBois.

Respiratory Infections in Myelomatosis. P. E. Baldry and J. E. Royds.

A Refrospective Clinical Study of Pulmonary Disease Due to "Anonymous Mycobacteria" in Wales. S. R. Kamat, C. E. Rossiter, and J. C. Gilson.

Volume 16, No. 3. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 9

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL.—4.30 p.m., 2nd Wiltshire Memorial Lecture by Dr. William Evans: To Tell Trash from Treasure.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. I. H. Mills: Control of Sodium Balance.

Tuesday, October 10

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Jarrett: Keratinization.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 3 p.m., Professor I. Donald: Neonatal Asphyxia.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8.30 p.m., Dr. Joan Stokes: Antibiotic Outlook.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. N. R. Butler: Murder at the Membranes, a National Study of Foetal Death.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. A. D. Gordon: Ultrasonic Rays in Neurology and Neurosurgery.

Wednesday, October 11

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Histology—Epidermal Hyperplasias and Verrucous Naevi.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. W. D. W. Brooks: Spontaneous Pneumothorax.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. R. C. Higham: Injuries of the Urinary Tract.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. B. E. C. Nordin: Calcium and Phosphorus Metabolism.

ROYAL SOCIETY OF HEALTH.—At Caxton Hall, Caxton Street, Westminster, S.W., 2.30 p.m., Dr. J. Greenwood Wilson: Imported Foods and the Nation—Some Problems.

WESTMORLAND COUNTY COUNCIL.—At County Hall, Kendal, 2 p.m., Miss G. Davies: Training for Childbirth.

WHITTINGTON HOSPITAL: ARCHWAY WING.—11.30 a.m., Professor R. Llewelyn Davies and Mr. Peter Cowan: Hospital and Community.

Thursday, October 12

ALFRED ADLER MEDICAL SOCIETY.—At 11 Chandos Street, London W., 8 p.m., Dr. W. Schindler: Significance of Puberty in Adult Neurosis.

BROOK GENERAL HOSPITAL.—5.45 p.m., Mr. G. B. Northcroft: Subdural Haematoma.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. B. Dowling: Classification of Eczema.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 11 a.m., discussion: Procidentia. Guest speaker: Mr. H. Roberts.

LONDON UNIVERSITY UNION SOCIALIST SOCIETY MEDICAL GROUP.—At Railway Union House, 7 p.m., Dr. Frank Gray: Future of Medicine and Dentistry in Great Britain.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Mr. Walpole Lewin: Vascular Lesions in Head Injuries.

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.—7.30 p.m., Professor F. Bergel, F.R.S.: Biological and Non-biological Models of Drug Receptors. A discussion will follow.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., Presidential Address by Sir George McRobert: From Empire to Commonwealth.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.

●WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Kensington Palace Hotel, 7.30 for 8 p.m., Presidential Address by Dr. A. Doyne Bell: A Brief for the Hospital Architect.

Friday, October 13

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.

KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.

LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., general meeting. Professor T. C. Gray: Some Highlights and Impressions of my Tour.

●LONDON HOSPITAL MEDICAL COLLEGE.—At the College Hall, Ashfield Street, E., 4.15 p.m., Schorstein Memorial Lecture by Dr. W. Evans: Cardiology at the London Hospital.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. R. B. Zachary: Neonatal Intestinal Obstruction; (2) 4 p.m., Sir Russell Brock: Present Position of Surgical Treatment of Cyanotic Heart Disease.

●ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—4.30 p.m., 11th Sir John Struthers Lecture by Sir Julian Huxley, F.R.S.: Evolution of the Higher Primates.

Saturday, October 14

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Recreation Room, Nurses' Home, Brighton General Hospital, 10.30 for 11 a.m., papers by Mr. R. H. F. Brain, Dr. B. G. Rigden, Mr. H. Clarke, and Dr. A. Macfarlane.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Bauer.—On September 17, 1961, at Lincoln County Hospital, Jacob Bauer, M.D., of The Old Rectory, Wellingore, Lincoln.

Corridan.—On September 18, 1961, at his home, 19 Broadlands Road, London N., Patrick Corridan, M.D., M.R.C.P.

Ede.—On September 11, 1961, at his home, Southlea, Redhill Lane, Worcester, William Edward Moore Ede, O.B.E., M.D., J.P., aged 86.

Heron Watson.—On September 13, 1961, at her home, Fuengirola, Spain, Frances Heron Watson (Mrs. Platt), M.B., Ch.B., D.P.H., late of Chichester, Sussex.

Hughes.—On August 17, 1961, at Pesaro, Italy, David Hughes, M.B., B.S., of Gyllyngdune, Dyserth, Flints, aged 26.

Macrae.—On September 15, 1961, at Rainford, Lancs, Kenneth William Duncan Macrae, M.B., Ch.B., aged 81.

McDiarmid.—On September 12, 1961, Neil McDiarmid, M.B., Ch.B., of 26b The Beach, Walmer, Kent, late of Arlesey, Beds.

Wood.—On September 4, 1961, Charles Albert Wood, *M.C.*, M.B., B.S., D.P.H., Colonel, I.M.S., retired, of "Bluegates," Bloxham, near Banbury, Oxon, aged 75.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Compulsory Examination for Notifiable Disease

Q.—*Is there any law under which an uncooperative patient believed to be suffering from tuberculosis can be compelled to undergo investigation?*

A.—Presumably the questioner has in mind a patient in whom possibly a 100-mm. *x*-ray film shows a picture highly suggestive of active pulmonary tuberculosis but who refuses to have further investigations—e.g., sputum examination—carried out. Section 172 of the Public Health Act, 1936 (as amended by the tenth schedule of the National Health Service Act, 1946) applies only to a person suffering from tuberculosis of the respiratory tract who is in an infectious state—i.e., has a positive sputum or laryngeal swab. Clause 34 of the Public Health Act, 1961, which comes into force on October 3, provides that on a written certificate issued by the district medical officer of health a justice of the peace may make an order for the medical examination of any person thought to be suffering from a notifiable disease. Before making such an order the justice of the peace will have to be satisfied that the person concerned is not under treatment by a registered medical practitioner or that the doctor treating him consents to the making of the order, which would, of course, cover the examination of the patient's sputum or of a laryngeal swab. Such powers are at present given in a number of local Acts, but this is the first time that they have appeared in general legislation.

Ephedrine in Heart Block

Q.—*Ephedrine hydrochloride is given to cases of complete heart block. What is its mode of action in these cases? I have found methylephedrine hydrochloride of great help in other types of case when the patient is sensitive to ephedrine, but owing to its lack of pressor effect, as compared with ephedrine hydrochloride, is it of any value in cases of complete heart block?*

A.—Ephedrine hydrochloride acts in complete heart block by increasing the force of contraction of the ventricular muscle and the ventricular rate. The blood-pressure rises mainly as a result of improved cardiac output. Methylephedrine hydrochloride is not widely used, probably, as the questioner suggests, because it has little pressor action. The pressor action is certainly important, for the blood-pressure tends to drop sharply with the development of complete heart block, and its maintenance may be vital for survival. The most satisfactory drug for treating complete heart block is isopropylnoradrenaline (isoprenaline), which may be given sublingually or by suppository. In acute emergency it may be given in very small dosage intravenously, and it has a powerful pressor action as well as increasing ventricular force and rate. At slow rates the pressor action may be sufficient to maintain an adequate cardiac output even though the increase in heart rate is not dramatic.

Megaloblastic Anaemia Due to Phenobarbitone

Q.—*Has a case of megaloblastic anaemia been reported as being due to the sole use of phenobarbitone? I know, of course, that this type of anaemia has been produced by such anticonvulsant drugs as phenytoin and primidone with or without an accompanying dose of phenobarbitone.*

A.—It is true that the majority of the reported cases of megaloblastic anaemia due to anticonvulsant drugs have been attributed to either primidone or phenytoin, or both, alone or in combination with a barbiturate. There is no doubt, however, that phenobarbitone alone can cause macrocytosis of the red cells,[1] and there is at least one well-authenticated case[2] in which megaloblastic anaemia occurred in an epileptic who was receiving phenobarbitone only. This patient had, however, been taking a much larger dose, 195–300 mg. (3–6 gr.) of phenobarbitone daily, than is usually prescribed. Other causes of megaloblastic anaemia were diligently sought for and could confidently be excluded. In another case[3] it is very probable that phenobarbitone was responsible for a megaloblastic anaemia. This patient had been taking 300 mg. of phenobarbitone daily for about twenty-five years, and although he had been given phenytoin for a month before he came under observation the history suggests that his anaemia was already established before this. There are also two additional case reports in which megaloblastic anaemia has been caused by other barbiturates—a combination of amylobarbitone and quinalbarbitone in one case[4] and methylphenobarbitone in the other.[5] It must be emphasized that megaloblastic anaemia is a rare toxic effect of anticonvulsant drugs, and that its occasional occurrence should not prevent the use of any of these drugs in ordinary therapeutic dosage whenever they are indicated.

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Reaction to Triple Antigen

Q.—*When a second dose of triple antigen has resulted in a severe local reaction (family history of hay-fever), is it safe to continue with diphtheria–tetanus prophylactic or should immunization be abandoned?*

A.—Despite a severe local reaction to the second dose of triple vaccine in a child (presumably of pre-school age) with a family history of hay-fever an attempt should be made to complete the triple immunization. In similar cases the third dose has sometimes been trouble-free. It would, however, be desirable to give a trial dose of 0.1 ml.; if no severe reaction occurred within 12 or so hours the rest of the dose (0.4 ml.) could safely be given on the following day. If a severe local reaction occurred after the test-dose it would be advisable to substitute diphtheria–tetanus vaccine (DT/Vac), since the cause of the trouble is almost certainly the pertussis component of the triple vaccine. The last thing to consider is the abandonment at this stage of the course of immunization against diphtheria and tetanus. Even a painful arm and a fretful child for a night are preferable to a child only half protected against these important infections.

Urticaria Associated with Sweating and Vasodilatation

Q.—*What might be the cause of urticarial weals appearing after a warm bath and persisting for about an hour in a girl aged 22? The water is soft, its temperature seems to make no difference, and only good-quality toilet soaps and no bath salts have been used.*

A.—Urticaria associated with heat, emotion, and exercise is probably due to the release of acetylcholine in the skin as the result of cholinergic stimulation of nerve fibres. Since this type of urticaria is always associated with both sweating and vasodilatation it may be due to some product of sweat-gland activity.[1] It would seem unlikely that the patient has urticaria due to any allergic or other cause. One presumes that she has not an eosinophilia.

REFERENCE

1 Herxheimer, A., *Clin. Sci.*, 1956, **15**, 195.

NOTES AND COMMENTS

Electrically Heated Insecticide Vaporizers.—Mr. J. G. S. H. Mitchell (Consumers' Association Ltd., London) writes: May I comment on an answer you gave to a question about insecticide vaporizers (" Any Questions ? " July 29, p. 324) ? More recent research[1] has shown that the safe level of output of continuous vaporizers may be rather higher than that recommended in 1951 by the Washington interdepartmental committee on pest control, and it has been suggested that for practical operation a dose of 0.2 g. per 1,000 cu. ft. (27 cubic metres) per 24 hours should be the limit. Different variants of this type of product are on sale to the general public as intermittent rather than continuous vaporizers. In a piece of unpublished research carried out in 1959 for the Consumers' Association, we found that while one branded product had a low output another, whose active ingredient was gamma B.H.C., had an output as high as 0.9 g. per hour. With such a high output it would not be advisable to use this product for more than an hour a week in any one room, and only then at a time when the room was likely to be unoccupied for six hours or more. The instructions accompanying this product did not mention precautions of this kind.

References

[1] Baker, A. H., Whitney, G. F. H., and Worden, A. N., *Laboratory Practice*, 1959, **8**, 3.

De Quervain's Disease.—Dr. J. M. Stanhope (Lutheran Mission, New Guinea) writes: I would like to comment on an answer concerning subacute thyroiditis (" Any Questions ? " May 27, p. 1556). In March of this year six patients sought treatment here for subacute thyroiditis. All were females, aged 20 to 40, and from the same village. They presented with fever, diffuse swelling of the thyroid gland, and pain for a period of one to two weeks previous to admission. As response to prednisolone on the part of the first patient was poor the other five were treated with thyroid gr. 1 twice daily in an attempt to put the gland at rest. Prompt relief of pain and fever was obtained and the swelling subsided over the next few days. Thyroid was given for two weeks, with gradual withdrawal of the drug in the second week. Four of the five treated with thyroid have remained well. One came back four weeks after discharge with a spherical swelling of the left thyroid lobe. At operation a unilocular cyst was found which histologically appeared to have resulted from localized haemorrhage. She is well at present, with the remaining half of her gland clinically normal.

Our Expert replies: Subacute thyroiditis is a self-limiting disease and may run a very mild and short course. It is therefore difficult to assess the comparative effectiveness of various forms of treatment. Treatment with thyroid hormone would seem logical because of its suppressive action on the gland. However, it has also been claimed that antithyroid drugs are effective, and these have the opposite effect. Most authorities would now agree that steroids offer the most effective treatment, and their apparent failure in only one case (cited by Dr. Stanhope) cannot be accepted as evidence against this view. It is interesting that one of Dr. Stanhope's patients developed a haemorrhage into a thyroid adenoma. Presumably the adenoma was present before the onset of thyroiditis, and the haemorrhage into it coincidental.

References

[1] Eylan, E., Zmucky, R., and Sheba, C., *Lancet*, 1957, **1**, 1062.

Nylon Hairbrushes.—Dr. A. Savill (London W.1) writes: Since 1958, when my article on the nylon brush was published,[1] I have received from several firms samples of safe nylon brushes (see " Any Questions ? " September 16, p. 778). These have rounded tips which do not injure the hair.

References

[1] Savill, A., *Brit. J. Derm.*, 1958, **70**, 296.

Malaria Prophylaxis.—Dr. B. Mornington (Burroughs Wellcome and Co., London N.W.1) writes: In the *Journal* of September 9 (" Any Questions ? " p. 721) the question of malaria prophylaxis was raised, and the expert's answer was in favour of proguanil (" paludrine ") because a person is less likely to forget to take a daily dose than a weekly dose of a prophylactic such as pyrimethamine (" daraprim "). As a rule a daily habit is perhaps a logical recommendation, but in practice we have witnessed embarrassment when the up-country traveller finds the medication has been left behind. This complication is minimized with a drug such as pyrimethamine which gives protection for at least a week and, for the rare occasion, a month. Incidentally, the African remembers his weekly dose by the slogan of " Sunday-Sunday " medicine, adopted for daraprim. The price factor may also speak in favour of a drug which is taken only once a week.

Our Expert replies: Dr. Mornington's admission of the logicality of the daily habit is noted, and the fact that the embarrassment has affected only forgetful travellers seems to indicate that the original suggestions will suit best the great majority of those taking malarial prophylactics.

Risks of Prolonged Stilboestrol Therapy.—Mr. E. Schleyer-Saunders (London W.1) writes: As the result of my study of the menopause, and having recently written about its management,[1 2] I am prompted to comment on the answer of your expert (" Any Questions ? " August 19, p. 534). I agree with his remarks that no evidence exists that prolonged oestrogen treatment has ever produced cancer in human beings. I must, however, contradict his statement that hot flushes cannot be cured and that the patient should be told that oestrogen is " only *postponing the evil day* " (my italics). It is generally accepted that the climacteric symptoms are the result of the cessation of ovarian function affecting also other endocrine glands. The gravity of the symptoms depends to a great extent on the emotional state of the patient. Consequently these women need reassurance and sympathy and not discouragement. In my experience, based on the treatment of over 500 menopausal women, the best results are achieved by implants of oestradiol and testosterone in a dosage depending on the vaginal cytological test and the condition of the uterus. The absorption of implants is slow and the withdrawal gradual. The flushes disappear within ten days and the patient experiences a feeling of well-being. In this way she is not reminded continuously of her condition as she would be by taking tablets regularly.

Our Expert replies: By taking certain words out of their context Mr. Schleyer-Saunders gives them a meaning different from that in the original answer. I agree with him that the mental attitude of the patient towards climacteric symptoms is of the greatest importance and that she requires sympathetic explanation rather than discouragement. As to providing hormones by subcutaneous or subfascial implants, this technique has obvious attractions in cases where hysterectomy has been performed. In the majority of women, however, the uterus is still present and its response to an oestradiol implant, with or without testosterone, is unpredictable. If uterine haemorrhage should result the tablet cannot usually be removed and the only way to control the situation may then be to carry out hysterectomy. This risk is so real that most authorities regard implants of oestrogenic hormones as unjustifiable in women who still have a uterus.

References

[1] Schleyer-Saunders, E., *Brit. med. J.*, 1960, **1**, 1274.
[2] —— *Med. Press*, 1960, **244**, 337.

Corrections.—In the comment by Drs. R. C. Nainby-Luxmoore and P. V. Cole on the oxygen content of mixture from the Minnitt machine (" Notes and Comments," September 23, p. 842) the reference should have been: Elam, J., in *Gas and Air Analgesia*, by R. J. Minnitt, 1st edition, 1938. Baillière, Tindall and Cox, London.

In the article, " Nasal Carriage of *Staph. aureus* by Newborn Babies " (August 5, p. 329), in the paragraph on " Nursing Procedures," the industrial methylated spirit used for the umbilical cords was industrial methylated spirit *B.P.C.* (19 vol. *ethyl* alcohol 95%, 1 vol. approved wood naphtha).

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